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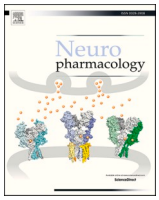

Gut-muscle-brain axis: Molecular mechanisms in neurodegenerative disorders and potential therapeutic efficacy of probiotic supplementation coupled with exercise

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ABSTRACT

Increased longevity is often associated with age-related conditions. The most common neurodegenerative disorders in the older population are Alzheimer's disease (AD) and Parkinson's disease (PD), associated with progressive neuronal loss leading to functional and cognitive impairments. Although symptomatic treatments are available, there is currently no cure for these conditions.

Gut dysbiosis has been involved in the pathogenesis of AD and PD, thus interventions targeting the "gut-brain axis" could potentially prevent or delay these pathologies. Recent evidence suggests that the skeletal muscle and the gut microbiota can affect each other via the "gut-muscle axis". Importantly, cognitive functions in AD and PD patients significantly benefit from physical activity. In this review, we aim to provide a comprehensive picture of the crosstalk between the brain, the skeletal muscle and the gut microbiota, introducing the concept of "gut-muscle-brain axis". Moreover, we discuss human and animal studies exploring the modulatory role of exercise and probiotics on cognition in AD and PD. Collectively, the findings presented here support the potential benefits of physical activity and probiotic supplementation in AD and PD. Further studies will be needed to develop targeted and multimodal strategies, including lifestyle changes, to prevent or delay the course of these pathologies.

1. Introduction

Life expectancy has progressively increased worldwide. Based on "The World population Prospects: The 2017 revision" of the United Nations, the number of people aged 60 or above is expected to triple by 2100, rising to 3.1 billion worldwide. In Europe, it has been estimated that 25% of the population is already aged 60 or above. As life expectancy increases, neurocognitive changes can also occur leading to a progressive decline in certain cognitive abilities, even though with some variability among individuals (Salthouse, 2009).

The most common form of dementia is Alzheimer's disease (AD), accounting for 60–70% of dementia cases. Cognitive decline in AD consists in three different stages, starting from a preclinical asymptomatic phase known as subjective cognitive decline (SCD), a symptomatic preclinical stage of mild cognitive impairment (MCI) and symptomatic clinical AD (Salthouse, 2009). The neuropathological hallmarks of AD brains include the deposition of extracellular plaques, mainly consisting of amyloid β peptide, and intracellular neurofibrillary tangles induced by hyperphosphorylated Tau. These pathological changes ultimately lead to synaptic dysfunction and neurodegeneration (Serrano-Pozo et al., 2011).

Parkinson's disease (PD) is the second most common neurodegenerative disorder (Ascherio and Schwarzschild, 2016), characterised by extensive loss of dopaminergic neurons in the substantia nigra with abnormal accumulation of α-synuclein, leading to the primary motor

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Abbreviations

AD	Alzheimer's Disease
APP	amyloid precursor protein
BDNF	brain derived neurotrophic factor
BMI	Body Mass Index
ERK	extracellular signal-regulated kinase
GSK3β	glycogen synthase kinase 3β
IFN-γ	interferon γ
IGF-1	insulin-like growth factor 1
IL-1	interleukin 1
IL-1β	interleukin 1β
IL-4	interleukin 4
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
HOMA-B	homeostatic model of B-cell function
HOMA-IR	homeostatic model of assessment of insulin resistance
HRR	heart rate reserve
LPS	lipopolysaccharide
MCI	Mild cognitive impairment
MDA	serum malondialdehyde
mTOR	mammalian target of rapamycin
NF kB	nuclear factor kB
NO	nitric oxide
6-OHDA	6-hydroxydopamine
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PPARγ	peroxisome proliferator-activated receptor γ
PS1	presenilin 1
QUICKI	quantitative insulin sensitivity check index
RCT	randomised controlled trial
SCD	Subjective cognitive decline
SCFA	short-chain fatty acid
SIRT-1	sirtuin-1
TAC	plasma total antioxidant capacity
TGF β	transforming growth factor β
TNF-α	tumour necrosis factor α
VO2 max	maximal oxygen consumption
VO_{2peak}	peak oxygen uptake

symptoms of PD, such as bradykinesia, tremor, postural instability and rigidity (Kalia and Lang, 2015). In addition, PD patients also display a broad range of non-motor symptoms, such as neuropsychiatric disturbances and cognitive impairments with deficits in working memory, language fluency, visuospatial processing and verbal learning (Goldman and Postuma, 2014). It has been estimated that up to 46% of PD patients diagnosed with MCI progress to Parkinson's disease with dementia (PDD) (Williams-Gray et al., 2013). Unfortunately, despite the considerable efforts made to elucidate the etiology of these devastating conditions and devise novel therapies, no preventative or disease-modifying strategies are available yet (Graham et al., 2017).

Interestingly, a recent study provided for the first-time strong evidence that unfavourable lifestyle modifiable factors (i.e., poor diet, smoking, lack of physical activity, alcohol misuse) can increase dementia risk, regardless of genetic factors (Lourida et al., 2019).

On these grounds, lifestyle interventions aimed at fostering healthy aging have increasingly become a matter of interest for the scientific community. In parallel, it is necessary to identify the biological and molecular factors underlying both healthy aging and pathological conditions to develop novel therapeutic strategies.

Over the last decade, a substantial body of evidence has led to the development of the "microbiota-gut-brain axis" concept, consisting of a two-way communication between the central nervous system, the gastrointestinal tract and gut microbiota (Morais et al., 2021). In the context of neurodegeneration, neuropathological studies showed accumulation of α-synuclein in the enteric nervous system and the motor nucleus of the vagus nerve during early stages of PD, thus providing the first link between PD etiology and the gastrointestinal system (Braak et al., 2006). Interestingly, gut dysfunction is a major manifestation of PD, preceding the onset of motor symptoms by several years (Cersosimo and Benarroch, 2012). A dysregulated gut homeostasis has also been recently observed in a mouse model of AD (Honarpisheh et al., 2020), whereas circulating bacterial metabolites positively correlate with amyloid deposition in AD patients (Marizzoni et al., 2020).

In parallel, a growing number of studies have also introduced the concept of "gut-muscle axis", consisting in a two-way interaction between the muscle and the gut microbiota (see (Ticinesi et al., 2019) and (Przewlocka et al., 2020) for review). Over the last years, physical exercise has become an appealing new potential venue for treatment of neurodegenerative disorders. Growing evidence has shown that different types of physical exercise could have a neuroprotective effect in aging and in neurodegenerative disorders (Santiago and Potashkin, 2023). However, it has yet to be determined in human subjects whether exercise-induced neuroprotection might be modulated by gut microbiota.

Human microbiota is a complex and diverse environment constituted by approximately 38 trillion of microbes, including bacteria, viruses, fungi, and archaea. Most of them are present in the gastrointestinal tract, especially the colon (Sender et al., 2016). A recent updated estimate found at least 2776 prokaryotic species in human gut (Bilen et al., 2018), representing a 28% increase in comparison with the previously published repertoire (Hugon et al., 2015). Among the phyla identified so far, *Proteobacteria*, *Bacteroidetes, Actinobacteria* and *Firmicutes* account for over 90% of gut bacteria, whereas other phyla, including *Fusobacteria* and *Verrucomicrobia,* appear to be less abundant (Bilen et al., 2018). The composition of gut microbiota is shaped during early childhood and depends on a variety of factors, such as delivery mode, breastfeeding, weaning and exposure to environmental bacteria. Gut microbiota is then fully established within 3 years of life to remain relatively stable throughout adulthood (Palmer et al., 2007). Brief exposures to stress, antibiotics or acute diseases can temporarily disrupt the microbiota, which is subsequently able to return to the previous composition (Relman, 2012). The level of microbiota diversity varies among individuals depending on health status, age, diet, genetics and lifestyle (Conlon and Bird, 2014).

The roles of gut microbiota are mediated by the production and release of various metabolic mediators that, once entered systemic circulation, can exert effects on other organs (Bermon et al., 2015) (Sharon et al., 2016). For instance, gut microbiota is involved in energy supply by mediating the breaking down of carbohydrates, lipids, and proteins. Bacteria also provide capacity for fermentation of resistant starches and dietary fibres thereby producing short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. At the intestinal level, SCFAs promote intestinal barrier integrity (Hiippala et al., 2018), mucus production (Finnie et al., 1995; Burger-van Paassen et al., 2009) and protect against inflammation (Hiippala et al., 2018; Correa-Oliveira et al., 2016). However, SCFAs also exert several beneficial roles at the systemic level, ranging from the modulation of systemic inflammation, induction of lipolysis, improvement of insulin sensitivity and increased energy expenditure via thermogenesis (van der Hee and Wells, 2021). In contrast, gut microbiota produces other molecules such as lipopolysaccharide (LPS) and trimethylamine-*N*-oxide that induce a pro-inflammatory status (Pascale et al., 2018). Gut bacteria also play a role in the synthesis of vitamins, including folate, vitamin B12 and

riboflavin with a pro-anabolic function (LeBlanc et al., 2013).

Remarkably, alterations in microbiota composition, commonly referred to as "dysbiosis", have been linked to several brain disorders, such as depression, AD, PD, and autism spectrum disorder. Thus, manipulation of microbiota has been proposed as possible therapeutic strategy (Sharon et al., 2019; Romano et al., 2021; Zhang et al., 2017; Cryan et al., 2020; Zheng et al., 2016).

However, despite this accumulating evidence suggesting a role of gut microbiota in a number of pathologies, the causality between dysbiosis and the diseases' onset is not fully understood due to the current paucity of interventional studies, such as faecal microbiota transplantation (Matheson and Holsinger, 2023). Moreover, longitudinal studies integrating clinical phenotypes and lifestyle factors might be useful to determine whether the observed changes in microbiota occur after the diseases' onset or were already present at a younger age and whether these changes could have been influenced by past lifestyle.

2. Exercise and gut microbiota: a two-way communication

2.1. Exercise-induced changes in gut microbiota

The first evidence for a possible modulation of microbiota by physical exercise came from Matsumoto et al. (2008) who found increased butyrate levels in the cecum of rats subjected to voluntary running exercise. A later study demonstrated that voluntary exercise could restore microbiota profile in obese mice fed with high fat diet (Evans et al., 2014). Recently, Yang et al. demonstrated that moderate-intensity exercise significantly increased *Bifidobacteria*, *Coprococcus* and *Clostridiales* in mice, that correlated with increased glucose, arginine, proline, and flavonoid metabolism (Yang et al., 2021).

In recent years, accumulating evidence from human studies also supports the key modulatory role of exercise on gut microbiota. Positive effects of exercise training have been reported in professional rugby players showing an increased diversity of the microbiota with higher proportions of *Firmicutes* and reduction in *Bacteroides* in comparison to sedentary high BMI (Body Mass Index) controls. These changes correlated with protein consumption and creatine kinase. In addition, the microbiota from both athletes and low BMI controls was enriched in *Akkermansia muciniphila* (Clarke et al., 2014). Further metagenomic analysis in professional rugby players identified an enrichment in species involved in the metabolism of amino acids and carbohydrate and SCFAs production (Barton et al., 2018). Similarly, professional cyclists compared to amateur level cyclists had a higher prevalence of *Prevotella* and *Methanobrevibacter smithii*, involved in energy and carbohydrate metabolism (Petersen et al., 2017). A recent study identified significant differences in the gut microbiome and metabolome across athletes from different sports classification groups, in the absence of dietary differences, indicating the role of training type and load in shaping microbiota (O'Donovan et al., 2020).

In non-athletes, taxonomic shifts towards health-promoting bacterial species have been reported in either pre-menopausal women undergoing brisk walking sessions (minimum 3 h/week) (Bressa et al., 2017) or endurance exercise without dietary changes in sedentary overweight women (Munukka et al., 2018). In addition, either sprint interval training or moderate intensity continuous training for 2 weeks could reduce *Firmicutes/Bacteroidetes* ratio as well as intestinal inflammatory markers in insulin resistant men (Motiani et al., 2020).

Both moderate and intense exercise sessions have been shown to produce beneficial effects on microbiota diversity. In a recent randomised controlled trial (RCT), sedentary lean and obese participants, both males and females, were subjected to a 6-weeks aerobic exercise intervention, consisting in 3 supervised sessions per week (30–60 min each) of moderate-to-vigorous intensity of aerobic exercise (60–75% of heart rate reserve, HRR). In this study, additional controls were implemented to ensure consistent dietary patterns (Allen et al., 2018). This intervention induced an enrichment of anti-inflammatory bacterial species of the *Firmicutes* phylum as well as an increased production of SCFAs only in lean subjects, thus suggesting the influence of body composition on exercise-induced microbiota's changes. Interestingly, this effect was completely reversed by 6 weeks of inactivity, suggesting that the importance of regular exercise to promote a healthy microbiota in the long term. In a 6-months RCT, sedentary overweight or obese participants were subjected to moderate aerobic exercise (50% of peak oxygen uptake ($VO_{2\ peak}$)), high intensity aerobic exercise (70% $VO_{2\ peak}$) or active commuting by bike and compared with a non-exercise group. Moderate and vigorous exercise, but not active commuting by bike, determined modest changes in alpha (within samples)-diversity, but no differences in the abundance of common genera (Kern et al., 2020). In accordance with Kern et al. (2020), but in contrast with Allen et al. (2018), Cronin et al. (2018) reported significant, but subtle, changes in alpha-diversity in healthy males and females after 8-weeks of moderate progressive aerobic and resistance program, performed 3 times a week. These contrasting findings could be due to the different training program or intensity of the aerobic exercise (see Table 1). It must be noted that the intensity is not always expressed in terms of heart rate reserve, thus further complicating the comparisons among the different studies. In addition, in Allen et al. (2018) a non-exercise group is lacking.

Another potential confounding factor in these studies is the impact of diet during the intervention. Diet is a well-known modulator of gut microbiome and could explain some changes observed in the microbiota of professional athletes (Clarke et al., 2014; Barton et al., 2018). However, in the interventional studies previously discussed, the dietary intake is either not reported (Motiani et al., 2020) or self-reported by the participants via food diaries (Munukka et al., 2018; Kern et al., 2020; Cronin et al., 2018). In Allen et al. (2018), the participants were required to follow a 3-days diet in consultation with a dietitian before faecal collections. However, specific details about the dietary pattern are not disclosed in this study. Therefore, in the future, controlled exercise interventions with or without standardized diets will be needed to separate the specific effects of exercise *per se* on the microbiota from the effects caused by different dietary patterns.

To date, a causal relationship between gut composition and exercise has not been demonstrated yet. Nevertheless, it has been hypothesised that different mechanisms could underlie exercise-mediated effects on microbiota.

It has been hypothesised that aerobic exercise could serve as hormetic stressor to induce positive adaptation over time (Keirns et al., 2020). In humans, even short sessions of treadmill running (20 min at 80% maximal oxygen consumption (VO2 max)) or 60 min at 65% VO2 max) increased intestinal permeability (Marchbank et al., 2011; Zuhl et al., 2014). Gut barrier disruption is also accompanied by a rise in inflammatory markers (Shing et al., 2014; Zheng et al., 2019). Several mechanisms may underlie this effect, including splanchnic hypoperfusion causing gut epithelial cells hypoxia (van Wijck et al., 2011) and hyperthermia possibly leading to tight junctions' disruption (Pires et al., 2017; Dokladny et al., 2016). In addition, strenuous exercise can lead to an increase in opportunistic pathogens at the expense of other taxa, as observed in a military training program (Karl et al., 2017). Profound changes in gut microbiota, with a higher abundance of pro-inflammatory species, were also observed in endurance runners (Morishima et al., 2021).

However, upon chronic aerobic exercise, gut adaptations seem to occur with positive changes in gut microbiota (Allen et al., 2018).

As opposed to aerobic training, resistance exercise does not seem to significantly impact the diversity and composition of gut microbiota (Bycura et al., 2021; Moore et al., 2022). In this regard, it is possible that a gut-stress threshold, necessary to induce significant perturbations in the gut microbiome, is not met by this type of exercise.

A recent systematic review assessed the influence of exercise type, frequency, duration and intensity on gut microbiota in human longitudinal interventions. Vigorous aerobic exercise was correlated to higher improvements in alpha and beta- (between samples) diversity, phylum

Table 1
Human intervention studies assessing exercise-induced changes in gut microbiota.

Reference	Subjects	Type of exercise	Intensity	Time	Frequency	Duration
Munukka et al. [46]	19 sedentary overweight women, average age: 36.8 ± 3.9 years.	Aerobic	A starting workload of 30 W on a cycle ergometer was increased by 20 W every second minute until 85% of subject's (HR_{max})	Week 1–2: 40 min cycling at low intensity and steady speed. Week 3–4: 50 min: sessions of 3 × 10 min interval training at moderate intensity were alternated with low intensity cycling at steady speed. Week 5–6: 60 min: 4 × 10 min intervals at moderate intensity.	3 times/ week	6 weeks
Motiani et al. [47]	26 sedentary subjects (17 with type 2 diabetes and 9 with pre-diabetes), 40–55 years old	Sprint interval training (SIT) and moderate intensity continuous training (MICT)	SIT: a starting workload of 50 W on a cycle ergometer was increased by 30 W every 2 min until volitional exhaustion. MICT: 60% of VO_{2peak} intensity.	SIT: 4–6 x 30 s bouts of all-out cycling efforts, with 4 min of recovery within bouts. Bouts was increased progressively from 4 to 6 after every other session. MICT: 40 min progressively increased by 10 min after every other session up to 60 min.	3 times/ week	2 weeks
Allen et al. [48]	18 lean subjects (average age: 25.1 ± 6 .52) and 14 obese subjects (average age: 31.14 ± 8.57)	Aerobic	Week 1–3: 60% of HRR. From week 4, intensity was increased by 5% of HRR per week up to 75% during week 6	Week 1: 30 min Week 2: 45 min Week 3–6: 60 min	3 times/ week	6 weeks
Kern et al. [49]	130 sedentary subjects, 20–45 years old	Aerobic (moderate or high intensity)	Moderate aerobic exercise: 50% of VO_2 peak High intensity aerobic exercise: 70% of VO_2 peak	Exercise was individually prescribed based on VO_2 peak and adjusted after 1, 1.5, 3 and 6 months.	5 times/ week	6 months
Cronin et al. [50]	90 sedentary subjects, 18–40 years old, BMI 22-35	Combined aerobic and resistance	Aerobic exercise: 5–7 out of 10 modified Borg RPE Resistance exercise: 3 sets x 8–12 repetitions. A starting load of 70% of 1 R M was increased by 15%–20% over 8 weeks	Aerobic exercise: increased from 18 min (week 1) up to 32 min (week 8).	3 times/ week	8 weeks
Bycura et al. [61]	49 healthy subject, 18–36 years old	Aerobic or resistance	Aerobic exercise: 60–90% of HRR Resistance exercise: 70–85% 1 R M. 3–6 sets of 6–12 total repetition	60 min	3 times/ week	8 weeks
Moore et al. [62]	14 males, 50–80 years old	Resistance	5 exercises, 3 sets of 10–12 repetitions with 1 min of rest between sets for each exercise	Not reported	2 times/ week	6 weeks

Abbreviations:VO_{2peak}:peak oxygen uptake HRR: heart rate reserve1RM:one-repetition maximumVO_{2max}: maximum rate of oxygen.

abundance and family abundance in comparison with low-to-moderate exercise. Four-to-five weekly sessions seem to be sufficient to induce changes in alpha diversity, while variations in beta diversity genus abundance are observed in two-to-three sessions per week. At the genus level, most of the changes were observed in exercise interventions lasting more than four weeks, and sessions lasting more than 90 min were associated with more robust changes in alpha diversity (Boytar et al., 2023).

In future, more research will be needed to verify these findings and elucidate the causal links between different exercise prescriptions and gut microbiota in order to develop appropriate interventions.

2.2. *Effect of gut microbiota on muscle physiology*

Preclinical studies support the hypothesis that gut microbiota can affect the physiology of skeletal muscle (Blanton et al., 2016; Yan et al., 2016; Siddharth et al., 2017; Lahiri et al., 2019; Hsu et al., 2015; Langille et al., 2014). In addition, several groups reported shifts in microbiota composition in patients with frailty syndrome and sarcopenia, further supporting the potential role of gut microbiota in regulating muscle mass and function (Kang et al., 2021; Ticinesi et al., 2020; Jackson et al., 2016; Zhang et al., 2020).

A possible mechanism by which bacteria can influence the skeletal muscle is by increasing amino acids availability. Overweight patients treated with a supplement containing soy protein and casein showed a change in microbiota metabolism towards amino acid degradation and fermentation, thus supporting the role of gut microbiota in anabolic processes (Beaumont et al., 2017). However, long-term protein supplementation can negatively affect gut microbiota by reducing health-promoting bacterial species, as reported by Moreno-Perez et al. (2018). In this study, cross-country runners in the protein group received 10 g of whey isolate and 10 g of beef hydrolysate diluted in commercial orange drink, containing 27.9 g of carbohydrates, for 10 weeks and showed a significant reduction in some bacterial species, including *Bifidobacterium*, *Roseburia* and *Blautia*. A recent observational study was carried out on bodybuilders and distance runners with different dietary patterns, obtained from each individual based on a 3-day food diary. Protein intake was significantly higher in the bodybuilders group, exceeding the reference intake with a protein: carbohydrate ratio twice as high as the distance runners and control groups. Conversely, the percentage of energy obtained from carbohydrates in the bodybuilders group did not fulfil the daily reference intake and was significantly lower than the other groups. These different dietary patterns influenced the relative abundance of several bacterial species among the athletes' groups. More specifically, high protein intake was associated with reduced SCFAs producers (Jang et al., 2019).

Microbiota-derived SCFAs may promote skeletal muscle renewal and reduce fat deposition into the muscle by increasing mitochondrial fatty acids oxidation. In this regard, it has been hypothesised that a dysbiotic gut may potentially underlie age-related muscle decline (Henique et al., 2015; Gumucio et al., 2019). A preclinical study in aging mice showed that the administration of butyrate increased muscle fibre cross-sectional area and reduced fat deposition into the muscle. In addition, the study reported an improved glucose metabolism and mitochondrial biogenesis after butyrate treatment. The authors hypothesised that these effects could be due to the inhibitory effect of butyrate on histone deacetylases, previously shown to be involved in muscle atrophy (Walsh et al., 2015).

Bacterial derived phenolic compounds have been recently shown to increase glucose uptake in muscle fibres *in vitro* (Houghton et al., 2019).

Conversely, microbiota-derived indoxyl sulphate has been associated with an upregulation of myostatin and atrogin-1, which negatively regulate muscle mass (Enoki et al., 2016).

3. Physical activity and neurodegeneration: role of muscle-brain axis

3.1. MCI and Alzheimer's disease

An increasing number of studies on AD models have shown the beneficial effect of physical activity on brain function. Several aerobic resistance training protocols have been used, employing treadmill running, swimming, or spinning wheels, with a variety of intensities, frequencies, and durations, thus demonstrating the current lack of a gold standard protocol (Lourenco et al., 2019; Zhang et al., 2018; Alkadhi and Dao, 2018; Wu et al., 2018; Lu et al., 2017; Koo et al., 2017; Moore et al., 2016; Haskins et al., 2016). Exercise-induced irisin has been recently implicated in the neuroprotective actions of physical exercise on synaptic plasticity and memory in AD mice (Lourenco et al., 2019). In addition, physical exercise could reduce inflammation, oxidative damage, and the accumulation of Aβ oligomers, which are responsible for the formation of amyloid plaques (Zhang et al., 2018; Wu et al., 2018; Lu et al., 2017; Koo et al., 2017; Moore et al., 2016). Amyloid burden was decreased possibly via the upregulation of sirtuin-1 (SIRT-1) which directed the processing of amyloid precursor protein (APP) toward the non-amyloidogenic pathway (Koo et al., 2017). Alkadhi et al. recently hypothesised that exercise-induced increase of brain-derived neurotrophic factor (BDNF) could shift the equilibrium of APP processing toward a non-pathogenic pathway (Alkadhi and Dao, 2018). Interestingly, high intensity treadmill running increased the abundance of SCFAs-producing bacteria and *Lactobacillus reuteri*, a vitamin B12 producer, in APP/presenilin 1 (PS1) mice. In addition, the exercise group showed reduced amyloid plaques (Abraham et al., 2019).

As opposed to aerobic exercise, the effect of resistance training exercise has not been extensively investigated in AD models so far. Reduction of Aβ burden and increased hippocampal insulin-like growth factor 1 (IGF-1) were observed in 3xTg AD mice subjected to weighted ladder climbing for 9 weeks (3 training sessions/week) (Pena et al., 2020). In addition, Hashiguchi et al. demonstrated that weighted ladder climbing for 4 weeks reduced the volume of Aβ plaques and restored intereleukin-1α (IL-1α), intereleukin-4 (IL-4) and intereleukin-6 (IL-6) to control levels in an APP/PS1 mouse model (Hashiguchi et al., 2020). In another study, ladder climbing for 4 weeks reduced hyperphosphorylated Tau and decreased the activation of microglia and astrocytes in 3xTg AD mice. These effects were accompanied by improved hippocampal memory (Liu et al., 2020).

A recent metanalysis of human studies found that physical activity was associated with decreased risk of all-cause dementia and AD, even in long follow-up studies (>20 years), thus supporting the role of physical exercise as protective lifestyle factor (Iso-Markku et al., 2022).

Nevertheless, clinical trials evaluating the effect of aerobic exercise on cognition produced mixed results, probably due to methodological differences, including disease stage, exercise modality, frequency, intensity, and duration (Bossers et al., 2015; Cancela et al., 2016; Holthoff et al., 2015; Morris et al., 2017; Hoffmann et al., 2016; Lamb et al., 2018; Toots et al., 2017; Law et al., 2014; Baker et al., 2010; Yu et al., 2021; Tsai et al., 2019). In addition, as for most of the studies in non-clinical populations, dietary intakes have not been considered as potential confounding factor. A recent metanalysis suggests that aerobic exercise has overall a moderate effect in delaying the decline of cognitive functions in individuals who have or are at risk to have AD (Panza et al., 2018). Considering the greater prevalence of AD and faster progression from MCI to AD in women (Podcasy and Epperson, 2016), potential gender differences have been investigated by Baker et al. (2010). Aerobic exercise-mediated improvement of memory and executive functions was more pronounced in women with MCI, despite comparable improvement in cardiorespiratory fitness and reduced body fat between genders. In addition, women in the aerobic exercise group showed improved glucose regulation and insulin sensitivity as well as decreased cortisol levels (Baker et al., 2010). Interestingly, an early study showed that the decline cognitive performance was related to higher cortisol levels specifically in women (Seeman et al., 1997).

Although less studied than aerobic exercise, progressive resistance training has been recently shown to improve attention, memory, and executive functions in MCI patients in a 6-months RCT and these effects persisted for 12 months post-intervention (Fiatarone Singh et al., 2014). The efficacy of this training protocol was subsequently shown to be mediated with structural plasticity in the posterior cingulate (Suo et al., 2016). In addition, resistance training counteracted volume loss of hippocampal areas up to 1 year after intervention (Broadhouse et al., 2020). Interestingly, a 16-weeks resistance exercise intervention was shown to increase IGF-1 and BDNF levels in the serum, while decreasing IL-15 (Tsai et al., 2019).

Collectively, these findings indicate that both aerobic and resistance exercise may be beneficial for older adults with mild-to-moderate AD. However, potential changes in gut microbiota induced by physical activity in AD patients still need to be addressed.

3.2. Parkinson's disease

The beneficial effects of aerobic exercise in different PD rodent models are supported by a vast literature (see (Crowley et al., 2019) for review). In particular, treadmill running or swimming training have been shown to improve motor symptoms and to provide neuroprotective effects (Goes et al., 2014).

The neurorestorative effects of exercise are likely to be due to increased expression of BDNF, but also to induction of downstream effectors, such as glycogen synthase kinase 3β (GSK3β) and the extracellular signal-regulated kinases (ERKs) (Choe et al., 2012; Tajiri et al., 2010). Decrease in neuroinflammatory markers and improved mitochondrial function have also been observed (da Costa et al., 2017; Tuon et al., 2015). A limited number of studies investigated the effect of aerobic exercise on non-motor symptoms. Depressive symptoms were reduced by forced treadmill and strength training (Tuon et al., 2014), while swimming or voluntary running were shown to restore memory deficits (Crowley et al., 2019; Goes et al., 2014). Crowley et al. (2019) also observed increased hippocampal neurogenesis induced by exercise.

In PD patients, a growing number of studies have demonstrated the beneficial effect of physical exercise on motor symptoms (Cugusi et al., 2015; Ferraz et al., 2018; Schenkman et al., 2018; Marusiak et al., 2019) (see Table 2). The recent Park-in-Shape RCT demonstrated that home-based and remotely supervised aerobic exercise in patients with mild PD improved motor function and cardiovascular fitness (van der Kolk et al., 2019), that is associated with increased frontoparietal connectivity (Johansson et al., 2022). A recent systematic review found that different exercise programs can also ameliorate global cognitive function, processing speed, sustained attention, and mental flexibility in PD patients at a mild-to-moderate stage with a 6-years clinical diagnosis. The larger improvement in cognition was observed for treadmill training performed 3 times/week for 60 min for 24 weeks (da Silva et al., 2018). It must be noted that none of the studies included assessments to control for possible differences in dietary patterns.

Considering the role of dysbiosis in PD (Huang et al., 2021), it would be interesting to determine whether the observed effects of exercise on PD symptoms may occur via modulation of gut microbiota. In this regard, a recent study demonstrated that aerobic training could decrease the levels of potential pathogenic species and the ratio of Firmicutes/Bacteroidetes in a mouse model of PD (Fan et al., 2022).

In addition, an observational study in PD patients assessed the composition of gut microbiota across ageing and in PD, also considering lifestyle factors, such as physical activity. Significant associations were found between moderate-to-vigorous physical activity and metabolic

Table 2
Human intervention studies assessing the effect of exercise on neurodegeneration.

Reference	Subjects	Type of exercise	Intensity	Time	Frequency	Duration
Baker et al. [103]	33 adults (17 women) with amnestic MCI, 55–85 years old	Aerobic	Intensity was increased during the first 6 weeks until participants were exercising at 75–85% of HRR.	45–60 min	4 times/ week	6 months
Fiatarone et al. [109] Broadhouse et al.[111]	100 adults with MCI (68% women). Average age: 70.1 ± 6.7 years	Resistance training plus computer-based cognitive training	Resistance training: 3 sets of 8 repetitions of each of 5–6 exercises per session. Progressive load: 1 R M every 3 weeks to maintain intensity at 3% from 80 to 92% of current maximum capacity.	60-100: 60 min control group, 75 min resistance or cognitive training group, 100 min combined group	2-3 times/ week	6 months
Tsai et al. [105]	55 adults with amnestic MCI, 60–85 years old	Aerobic or resistance	Aerobic: 50–60% of HRR during the first 2 weeks, 70–75% for the rest of the program Resistance: 60–70% of the individual target 1 R M during the first 2 weeks, 75% of their individual target for the rest of the program.	40 min including warm up and cool down (30 min intervention)	3 times/ week	16 weeks
Cugusi et al. [119]	20 patients (16 men, 4 women) with idiopathic PD (Hoehn and Yahr stage 1–3). 40–80 years old, on stable dopaminergic medication	Aerobic	60–80% of HRR	60 min	2 times/ week	12 weeks
Ferraz et al. [120]	62 patients (37 men and 25 women) with idiopathic PD (Hoehn and Yahr stage 2–3) Average age: 69 ± 5 years old	Functional training, aerobic exercise, or exergaming involving strength and muscular endurance	Aerobic exercise: 50% of HRR (week 1), 55% of HRR (week 2–3), 65% of HRR (week 4–5), 70% of HRR (week 6–7), 75% of HRR (week 8).	Aerobic exercise: 50 min including warm up and cool down (30 min intervention) Functional training: 30 min (3 min x each activity) Exergaming: 30 min	3 times/ week	8 weeks
Shenkman et al.[121]	128 patients with idiopathic PD (Hoehn and Yahr stage 1–2), naïve to dopaminergic medication, 40–80 years old	Aerobic	High intensity group: 80–85% of HRR Moderate intensity group: 60–65% of HRR	50 min including warm up and cool down	4 times/ week	6 months
Marusiak et al.[122]	20 patients with idiopathic PD (Hoehn and Yahr stage 1.5–3), 60–90 years old	Aerobic interval	60% of HR_{max} during the first week, that is increased by 5% every two weeks	40 min, 8 sets of 5 min intervals (3 min of cycling at ≥ 60 rpm, 2 min of cycling at < 60 rpm)	3 times/ week	8 weeks
Van der Kolk et al. [123]	130 PD patients (Hoehn and Yahr stage 2 or lower), 30–75 years old, on stable dopaminergic medication, assessed off medication	Aerobic	The lower boundary of heart rate was set to 50–70% of HRR and gradually increased during the intervention to the upper boundary of 80% of HRR	45 min including warm up and cool down (30 min intervention)	3 times/ week	6 months

Abbreviations:HRR: heart rate reserve, 1 R M: one-repetition maximum, RPE: rating of perceived exertion, HR_{max}:maximal heart rate.

pathways related to the synthesis of various quinones, but only in healthy older adults (Nuzum et al., 2023). Therefore, further research and RCTs in patients will be necessary to clarify the causative links between exercise, gut microbiota, and the amelioration of PD symptoms.

4. Probiotics supplementation in AD and PD

4.1. MCI and Alzheimer's disease

Few intervention studies were carried out in AD models administered with probiotics. For instance, Bonfili et al. assessed AD mice in a range of cognitive and anxiety tests after a 4-months administration of a probiotic blend (SLAB51) containing nine strains of *Bifidobacterium*, *Lactobacillus* and *Streptococcus thermophilus*. The authors reported improvements in cognitive performance as well as reduced anxiety in the treatment group. Interestingly, these changes were associated with reduced accumulation of amyloid and partial restoration of two impaired neuronal proteolytic pathways, namely the ubiquitin proteasome pathway and autophagy (Bonfili et al., 2017). In another mouse model, the administration of a strain of *Bifidobacterium breve* for 6 days could prevent memory deficits and reduce the expression of pro-inflammatory genes in the hippocampus (Kobayashi et al., 2017). Moreover, a study reported an amelioration of spatial memory and oxidative stress in a mouse model of AD treated for 8 weeks with a probiotic blend of *L. acidophilus*, *L. Fermentum*, *B. Lactis* and *Bifidobacterium longum* (Athari Nik Azm et al., 2018).

In humans, there are preliminary intervention studies investigating the effect of probiotics on cognitive status in patients with MCI or AD. A clinical trial assessed the cognitive functions and metabolic status of 60 AD patients administered with either milk or probiotic milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidus* and *Lactobacillus fermentum* for 12 weeks (Akbari et al., 2016). The authors found that the treatment with probiotic milk positively affected cognitive functions as well as some markers of metabolic status. For instance, the treatment with probiotic milk substantially affected lipid profile and factors involved in the metabolism of carbohydrates. Serum triglycerides were substantially decreased in the intervention group as well as the homeostatic model of assessment for insulin resistance (HOMA-IR), the homeostatic model of B-cell function (HOMA-B) and serum high sensitivity *C*-reactive protein. Conversely, quantitative insulin sensitivity check index (QUICKI) was significantly increased. In terms of oxidative stress markers, serum malondialdehyde (MDA) was reduced in the intervention group, but nitric oxide (NO) and plasma total antioxidant capacity (TAC) were unchanged. In contrast with these results, in a more recent paper, the same researchers could not find any significant effect of probiotic supplementation on either cognition or inflammatory and oxidative markers in patients diagnosed with severe AD, suggesting that the stage of the disease can significantly impact the

outcome of the treatment thus the timing of intervention might be crucial (Agahi et al., 2018).

In another RCT, Hwang et al. assessed the effectiveness of an early intervention with probiotics in patients with MCI. 100 subjects were randomly administered with a placebo or with Lactobacillus plantarum C29-fermented soybean. The intervention group showed an amelioration of cognitive functions especially in the attention domain, that was associated with increased in serum levels of BDNF (Hwang et al., 2019).

Another research group investigated the effect of a single bacterial strain, *Bifidobacterium breve* A1, on cognitive function in patients with MCI in an open label, single-arm study (Kobayashi et al., 2019a) and subsequently in an RCT (Kobayashi et al., 2019b). After 12 weeks treatment with the probiotic, the authors observed an improvement in the subscale "immediate memory" score only in the subjects with low scores at baseline (Kobayashi et al., 2019b).

Moreover, combined probiotic and selenium supplementation for 12 weeks has been shown to improve cognitive functions in AD patients and some metabolic markers. In particular, serum high sensitivity *C*-reactive protein, HOMA-IR, LDL cholesterol, total/HDL cholesterol ratio and serum triglycerides were decreased by the co-supplementation, whereas total glutathione and QUICKI were increased (Tamtaji et al., 2019a).

In a recent clinical trial, supplementation with a strain of *Bifidobacterium brevis* for 24 weeks ameliorated cognitive functions in MCI patients on some subscales scores, but not total scores, and suppressed brain atrophy progression (Asaoka et al., 2022).

4.2. Parkinson's disease

Increasing evidence in preclinical models support the neuroprotective effects of probiotics and their efficacy in ameliorating motor dysfunctions in PD. In a 6-hydroxydopamine (6-OHDA) mouse model of PD, the probiotic formulation SLAB51 was administered for 2 weeks before the 6-OHDA injection and for additional 3 weeks following the toxin injection. This probiotic formulation exerted a neuroprotective action against the loss of dopaminergic neurons in the substantia nigra, in addition to its anti-inflammatory and antioxidant activity (Castelli et al., 2020). Neuroprotective effects and improved motor function, along with improved muscle mass, were observed in a 6-OHDA rat model after 8-weeks supplementation with *Lactobacillus salivarius*. Interestingly, these effects were accompanied by increased SCFAs in faecal samples, increased mitochondrial activity in the muscle and brain and elevated generation of antioxidants in the serum (Nurrahma et al., 2021). In another murine model of PD, administration of *Lactobacillus plantarum* and two strains of *Streptococcus thermophilus* for 22 days significantly reduced neurodegeneration with a positive effect on motor behaviour. These effects were accompanied by decreased levels of inflammatory cytokines IL-6 and tumour necrosis factor α (TNF-α) and increased levels of anti-inflammatory cytokine interleukin-10 (IL-10) in serum and brain (Perez Visnuk et al., 2020).

PD is also associated with non-motor symptoms, including cognitive impairments, anxiety, depression, and sleep disorders that negatively affect quality of life. These symptoms precede the onset of motor dysfunctions and continue as the disease progresses. However, the effects of probiotics on neuropsychiatric aspects of PD have not been extensively investigated so far. Recently, Xie and Prasad explored the efficacy of *Lacticaseibacillus rhamnosus* in a 6-OHDA rat model of PD on non-motor symptoms. An improvement in hippocampal-dependent cognition, but not anxiety, was observed in PD rats after 7-weeks supplementation (Xie and Prasad, 2020).

In humans, few clinical trials demonstrated the efficacy of probiotic supplementation as a treatment of constipation, a very common symptom in PD potentially leading to serious complications (Georgescu et al., 2016; Barichella et al., 2016; Tan et al., 2021). In addition, multistrain probiotics supplementation for 12 weeks improved gene expression of IL-1, IL-8, TNF-α, transforming growth factor β (TGF-β) and peroxisome proliferator-activated receptor γ (PPAR-γ) in PD patients (Borzabadi et al., 2018) and ameliorated metabolic profile (Tamtaji et al., 2019b). However, the effect of probiotics on motor and non-motor symptoms has not been adequately investigated. So far, one RCT reported improved symptoms in PD patients after 12 weeks of probiotic supplementation. The disease severity was evaluated as Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total scores (Tamtaji et al., 2019b). To be noted, physical activity levels have not been recorded and considered as a potential confounding factor.

Moreover, a double-blind placebo-controlled study (SymPD, NCT05146921) is still ongoing in the UK to test the efficacy of a multistrain probiotics on PD symptoms and to evaluate the changes in gut microbiota and blood inflammatory markers.

5. Probiotic supplementation and muscle health

Considering the reciprocal influence of gut microbiota and muscle physiology, probiotic supplementation may represent a novel strategy to optimize muscle functionality and metabolism in either anabolic (exercise) or catabolic (sarcopenia and cachexia) conditions. In healthy rodent models, 6 weeks supplementation with *L. plantarum* improved muscle mass, forelimb strength and swimming endurance, while decreasing serum lactate, ammonia, creatine kinase (CK) and glucose after acute exercise (Chen et al., 2016). Moreover, 3–4 weeks treatment with *B. longum* or *L. salivarius* isolated from weightlifting athletes' gut microbiota improved muscle mass and swimming endurance in mice. This effect correlated with decreased anti-fatigue markers, such as lactate, ammonia and CK (Lee et al., 2019, 2020) and improved hepatic and muscular glycogen storage (Lee et al., 2020). Another study demonstrated that heat-killed *B. breve* B-3 (B–3HK) enhanced muscle mass and grip strength in mice. From the metabolic point of view, B–3HK significantly increased mitochondrial biogenesis pathways (Toda et al., 2020).

Supplementation with different probiotic strains in endurance athletes and soldiers is also well-documented. In general, these studies have shown the anti-inflammatory properties of *L. fermentum*, *L. plantarum*, *B. subtilis* and *B. coagulans*, with a reduction of pro-inflammatory cytokines TNF-α, IL-6, interferon-γ (IFN-γ) and an increase in anti-inflammatory cytokines, including interleukin-10 (IL-10) (Cox et al., 2010; Hoffman et al., 2019; Huang et al., 2019). Moreover, *B. coagulans*, *L. plantarum* and *Spirulina platensis* were shown to promote muscle recovery after exercise (Huang et al., 2019; Jager et al., 2016).

In terms of muscle performance, different probiotic strains, including *B. coagulans*, *L. plantarum* and *Spirulina platensis*, were shown to improve exhaustive endurance (Hoffman et al., 2019; Huang et al., 2019). However, probiotics do not seem to significantly affect physical performance (Shing et al., 2014; Cox et al., 2010; Hoffman et al., 2019; Toohey et al., 2020; Carbuhn et al., 2018).

Rodent models of cancer and ageing have been used to study the effect of probiotics in catabolic states. Supplementation with L. *gasseri* and *L. reuteri* was shown to reduce the loss of skeletal muscle mass and increase fibre size. (Bindels et al., 2012; Varian et al., 2016). These effects were supposed to be mediated by inhibited proteolysis (Bindels et al., 2012) and increased protein synthesis with enhanced phosphorylation of protein kinase B (also known as AKT) and mammalian target of rapamycin (mTOR) (An et al., 2019).

Human studies conducted so far have reported a reduction of inflammation in cancer patients or in the elderly after probiotic supplementation but did not directly measure muscle mass and function (Spaiser et al., 2015; Fong et al., 2020).

6. May probiotic supplementation and exercise have a synergistic effect to control neurodegenerative diseases?

Considering the influence of both gut microbiota and the muscle on brain functions and the crosstalk occurring between these systems, it is reasonable to hypothesise a synergistic effect mediated by a combined

intervention with probiotics and exercise training. However, to date, there is limited evidence addressing this aspect. The administration of *B. Bifidus* and L. *plantarum* in combination with treadmill running for 8 weeks significantly improved spatial learning, while reducing Aβ neurotoxicity, in a rat model of AD (Shamsipour et al., 2021). Another recent study investigated the combined effect of probiotics and exercise in an APP/PS1 mouse model of AD. The authors showed that interval treadmill running, and probiotics intervention for 20 weeks could ameliorate memory deficits with decrease of amyloid plaques. In addition, this combined intervention, but also exercise alone, induced a shift in the microbiota towards butyrate and vitamin B12 producers (Abraham et al., 2019). These preliminary findings suggest the potential synergistic effect of probiotics and exercise, although more studies will be needed to further corroborate this evidence.

7. Conclusions

The social and economic burden of neurodegenerative disorders demands novel and multidimensional approaches to prevent and delay these pathologies and lower the morbidity. Evidence discussed in this review generally supports the role of gut microbiota in the pathogenesis of AD and PD. Nevertheless, further research will be needed to dissect the cause-effect relationship between the microbiota alterations and neurodegenerative disorders, possibly considering also gender differences. Another limitation evidenced by the available literature is the current lack of longitudinal studies, due to their challenging nature in the context of aging especially in human subjects. Thus, it is still unknown whether the dysbiotic profile in the elderly population with neurodegenerative disorders was acquired at a younger age or after the disease onset. In addition, the potential shifts in microbiota's composition throughout the different stages of the disease still need to be elucidated.

Evidence discussed in this review also supports the existence of a "gut-muscle axis", where exercise significantly shapes the gut microbiota and, on the other hand, gut bacteria can affect muscle physiology. Lifestyle factors, including moderate-to vigorous exercise, and probiotic supplementation have been shown to promote microbiota's diversity and beneficial bacterial species, with potential implications for disease prevention and treatment. Nevertheless, the available studies presented in this review also show some limitations. For instance, confounding factors potentially affecting the gut microbiota are not considered in most of the studies (i.e., physical activity levels when studying the effect of probiotic intervention, diet when assessing the effect of exercise training). In addition, long-term case control studies are still needed to identify the time-window where the subjects are most likely to benefit from the intervention. Long-term follow up longitudinal studies will be useful to further support the protective role of exercise or probiotic intervention against cognitive decline. Much more work is also required to tailor probiotic therapies to the individual patients, based on their microbiota profiles. In this regard, the recent advances and increasing availability of multiomics approaches hold potential to promote personalised therapies, in line with the shift toward precision medicine.

Overall, the studies reviewed here may support the existence of a "gut-muscle-brain axis" where both nutritional factors and exercise have converging effects on brain functions, as summarized in Fig. 1.

Probiotic supplementation as well as regular exercise have shown promising effects on cognitive performance in AD and PD patients. A putative mechanism is the re-shaping of gut microbiota induced by both probiotics and physical activity with subsequent SCFAs production and neuroprotection. Moreover, components of the muscle secretome may affect neurogenesis and brain vascularization. However, it must be noted that research in this field has sometimes produced mixed results, probably due to the cognitive tasks employed, the different types and intensities of exercise training and the individual level of cognitive reserve of the participants. In addition, based on the available studies there is no conclusive agreement about the most beneficial type of exercise to prevent cognitive decline.

Finally, clinical trials involving a combination of probiotic supplementation and exercise training will be needed in future to determine whether these interventions can synergistically interact and amplify their individual effects on cognitive performance.

In conclusion, elucidating the molecular mechanisms underlying the

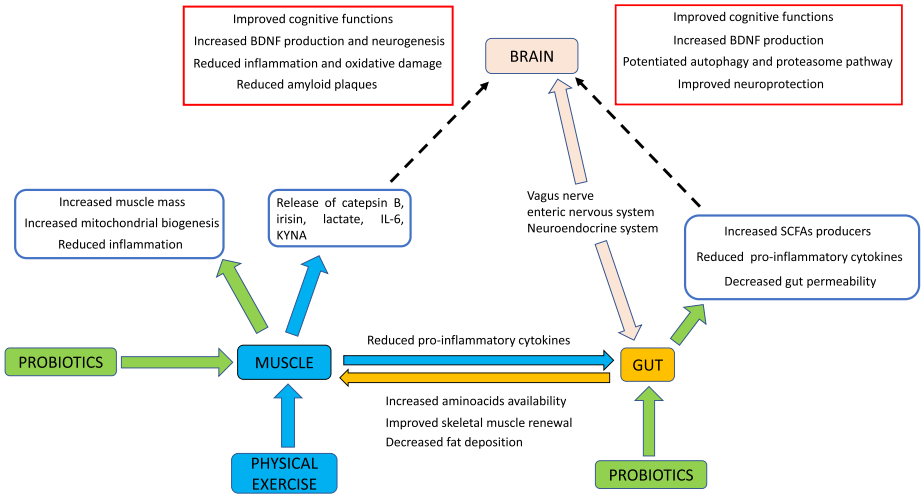

Fig. 1. Effects of probiotics and exercise on the gut-muscle-brain axis and possible implications for neurodegenerative disorders. A bidirectional pathway of communication exists between the brain and the gut via the vagus nerve, the neuroendocrine system and the enteric nervous system. The neuroprotective action of probiotics may be mediated by reduced inflammation and SCFAs-producing bacteria. SCFAs can decrease gut permeability thus preventing the release of toxins into the systemic circulation. In addition, SCFAs can also improve the blood brain barrier integrity. A healthy gut microbiota can positively affect the muscle physiology. In particular, probiotic supplementation has been shown to increase muscle mass and mitochondrial biogenesis, while reducing inflammation. In addition to its anti-inflammatory effects, exercise triggers the release of several factors, such as BDNF, catepsin B, irisin and lactate with crucial role in BDNF expression, neurogenesis and vascularization. Exercise-induced production of kynurenic acid (KYNA) prevents the accumulation and the toxic effects of kynurenin. The coloured arrows represent pathways regulated by probiotics (in green), by gut microbiota (in orange), by physical exercise and the muscle (in blue) and by the brain (in light pink). The dashed arrows represent the potential pathways between the muscle and the brain, or the gut and the brain, that might be implicated in cognitive potentiation and neuroprotection.

"gut-muscle-brain axis", understanding how these pathways are intertwined and how they become deranged in pathological conditions may lead to the identification of novel pharmacological targets. On the other hand, from a public health perspective, in depth-understanding of the effects exerted by specific nutritional approaches and exercise training on the "gut-brain-muscle axis" could provide structured standard strategies for a cost-effective, non-invasive approach to prevent and/or delay neurodegeneration.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

No data was used for the research described in the article.

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