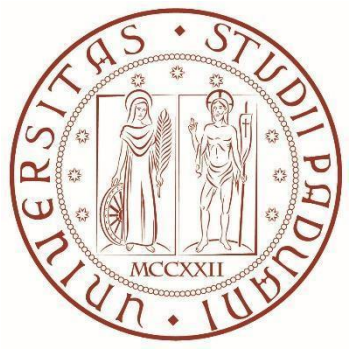

UNIVERSITÀ DEGLI STUDI DI PADOVA

Dipartimento di Scienze Biomediche

Corso di Laurea Triennale in Scienze Motorie

Tesi di Laurea

ON THE NEUROPROTECTIVE ROLE OF MYOKINES INDUCED BY RESISTANCE TRAINING IN ADULTS WITH MILD COGNITIVE IMPAIRMENT

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GOAL OF THE THESIS

This study aims to disclose the findings that support the role of exercise in the improving cognitive traits in the elderly. The main objective of this thesis is, in particular, to assess current evidence that validates the release of myokines from skeletal muscles during and after exercise, especially resistance training, to slow the progression of neurodegenerative diseases in older people with already diagnosed mild cognitive impairments (MCIs). This study illustrates the potential for myokines to become exercise's molecular parameters to track nervous system capacity ameliorations.

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1.1 NEURODEGENERATIVE DISEASES

1.1.1 Impact of neurodegenerative diseases

As the mean population's age increases through the years, western countries have to deal with the need of treatments and therapy, caregivers and hospitalisation. This represents a burden for patients and their relatives, economically speaking and for more practical everyday reasons. Besides that, ageing is often associated with a higher risk of life-threatening conditions, including cancer, cardiovascular disease and neurodegeneration (Niccoli 2012).

Their prevalence seems to be rapidly increasing worldwide and its prime association is age. To be more precise, according to the World Health Organization dementia seems to be the seventh cause of death worldwide. (World Alzheimer Report 2021)

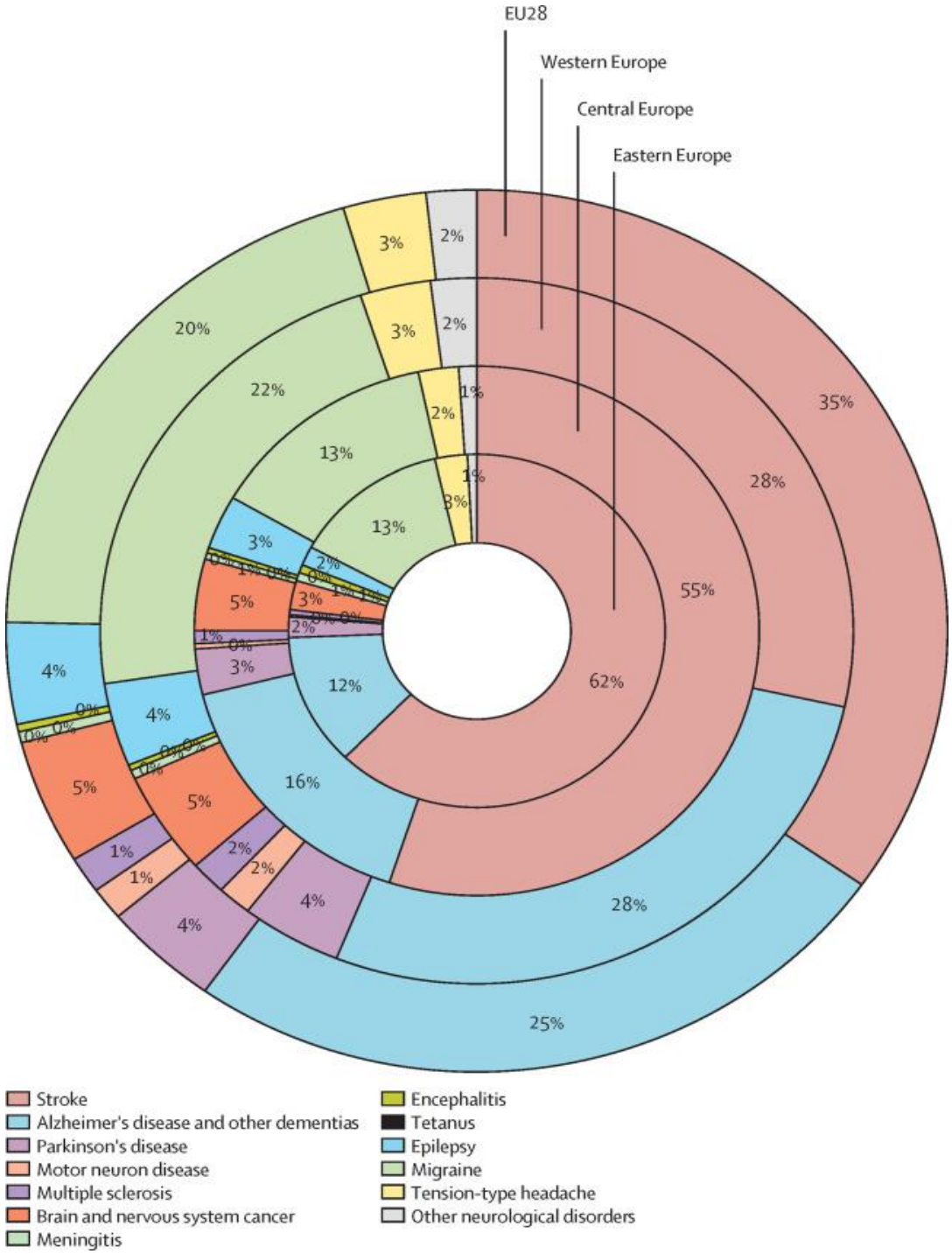

Figure 1: Contribution of each disease to the overall burden of neurological disorders in the EU28, western, central, and eastern Europe in 2017 Percentages represent the proportion of DALYs.

DALYs=disability-adjusted life-years. EU28=the 27 countries in the EU plus the UK. (Deuschl et al. Lancet Public Health. 2020.)

If we keep Stroke and Encephalitis out, it leaps out how Dementia and Alzheimer's Disease are present in the European Community, with neurological disorders being ranked third for disability-adjusted life-years and deaths. This could be explained in part by the long life expectancy in Europe and also the increasingly long duration of these ageing-related maladies. Nevertheless, data reminds us of the burden neurological disorders, of which risk factors are not completely understood.

1.1.2 Common neurodegenerative diseases

Most common neurodegenerative disorders, or types of Dementia are Alzheimer's Disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ASL) which all have in common brain protein aggregation and misfolding until neuronal death. (Paraskevaidi 2018, Checkoway 2011)
Other types of Dementia are:

- Creutzfeldt-Jakob disease (CJD), which is the most common human form of a group of rare, fatal brain disorders known as prion diseases.
- Dementia with Lewy bodies (DLB). Lewy bodies are composed primarily of Alpha-synuclein protein, which is found widely in the brain, but its normal function isn't yet known.
- Mixed Dementia, when people have brain changes of more than one type of dementia, for example Lewy bodies coexisting with brain plaques and tangles.
- Frontotemporal dementia (FTD), which includes Amyotrophic lateral sclerosis (ALS).
- Korsakoff syndrome, which is a chronic memory disorder caused by severe deficiency of thiamine (vitamin B-1). Korsakoff syndrome is most commonly caused by alcohol misuse, but certain other conditions also can cause the syndrome.
- Vascular Dementia, which is caused by conditions that block or reduce blood flow to various regions of the brain, depriving them of oxygen and nutrients.

Informations for "Types of Dementia" come from Alzheimer's Association internet site.

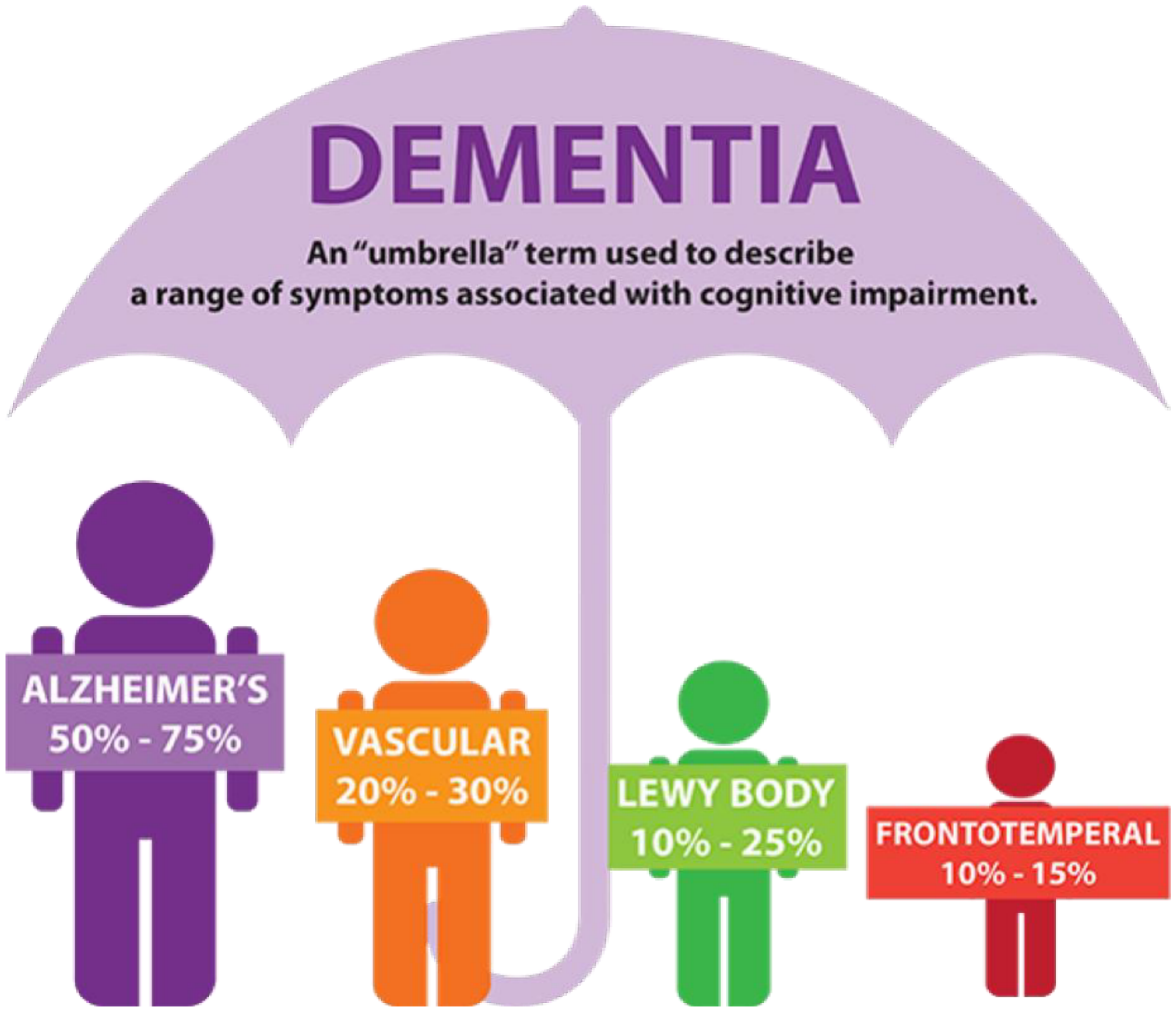

Figure 2. This picture shows percentages of people affected by different types of Dementia. (Dementia Friendly Wyoming)

1.1.3 Main mechanisms of neuronal cell loss

What we call Dementia is a loss of cognitive function. Neurodegeneration leads to irreversible structural and functional damage of all neurons that may evolve into cell death. It is associated with synapses and neural network dysfunctions, with the exception of changes in brain proteins. These diseases may affect different sensory, motor and cognitive functions of individuals such as movements, words, memory, intelligence, and many others, including intracellular and intercellular mechanisms. To go into further details, we should briefly examine the mechanisms of neuronal cell death. In general, mature CNS neurons are more resistant to cell death than neuronal precursors because they can cope with different stresses

and maintain cell homeostasis. It seems that there is no internal clock that determines the length of a neuron's life.

In Physiological Conditions, neurogenesis in an adult CNS is often accompanied by neuronal cell death as an extension of the neurogenesis's development. Failed neurons often undergo apoptosis and are eliminated by microglia.

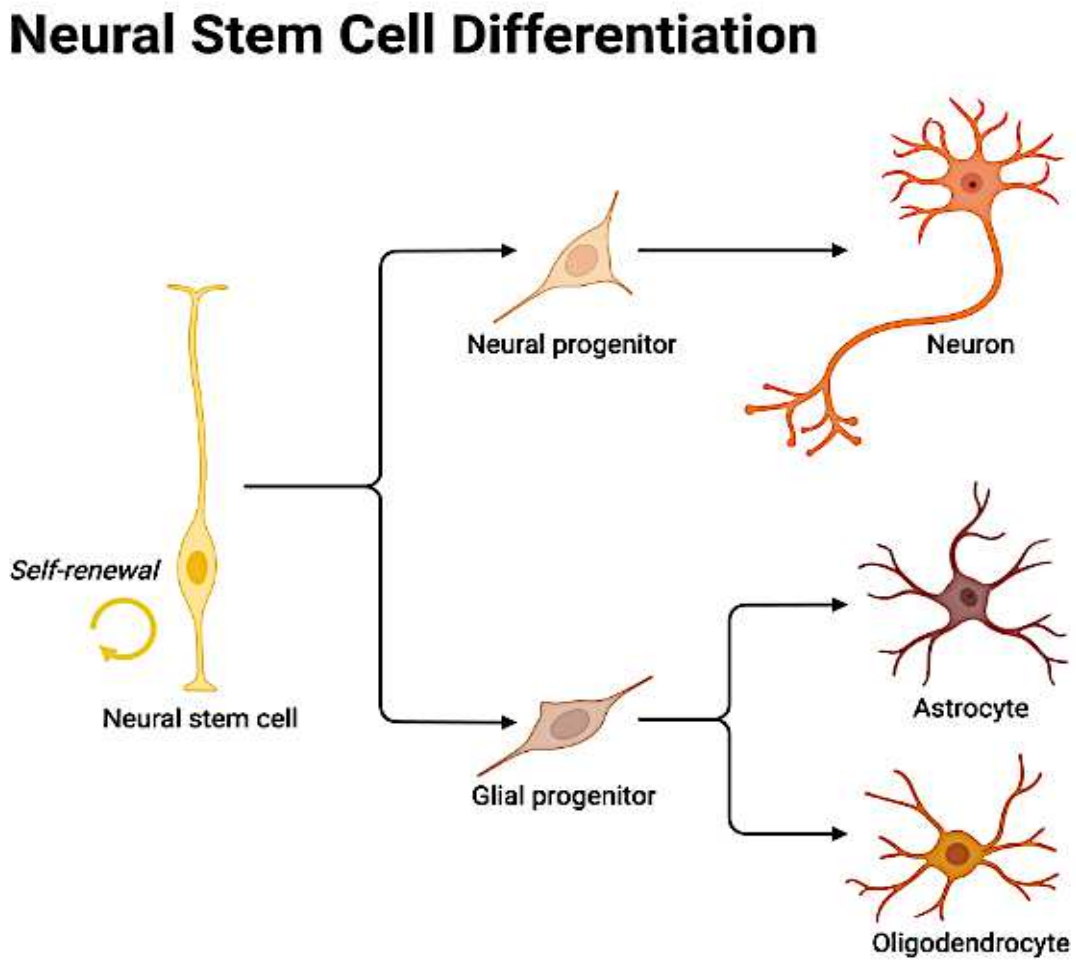

Figure 3. A simplified model of neural stem cell (NSC) differentiation.
NSCs can be committed toward either neuronal- or glial-restricted progenitors. Neuronal precursors differentiate into several types of mature neurons while glial precursors can give rise directly to astrocytes or to O-2A progenitor cells, which in turn differentiate either in astrocytes or oligodendrocytes. (Tang 2017)

Cell death is the final solution for a neuron only when the amount of stress it faces goes beyond the cell's recovery capacity, a circumstance that is commonly seen in

neurodegenerative diseases. This differs from acute strokes which cause a sudden decline of energy production in the affected neurons and consequently, elicits acute neuronal cell death.

In pathologic conditions, neurodegeneration can be linked to pathological protein formation and, in many cases, high-order aggregate formation. This often places stress on neurons and renders subsequent cytotoxic events, which include an increased number of reactive oxygen species (ROS), excitotoxicity, synaptic dysfunction, impaired protein degradation systems, endoplasmic reticulum (ER) stress, DNA damage, mitochondrial dysfunction, inflammation and cell cycle re-entry.
However, the underlying signalling mechanisms of how these factors induce the initiation of cell death remain elusive. (Hao Chi 2018)
Protein aggregates are not typically found in healthy brains, which is common in many neurodegenerative pathologies. Nevertheless it is still unclear whether some aggregates are by-products or even have protective effects against cell death. (Hao Chi 2018)
Apoptosis and necrosis are believed to be the two major death pathways for neurons. Apoptosis is a type of programmed cell death process (PCD) which occurs to a large extent in tissues that need remodelling while growing. It can be incited by signals, either extrinsically through binding of cell death receptors and the stimulation of extracellular ligands or intrinsically via internal stimuli, such as the p53 pathway upon DNA damage. Both pathways alter the permeability of the inner mitochondrial membrane leading to release of specific factors from mitochondria into the cytosol. In turn, these factors, including the cytochrome c, promote the triggering of caspase cascade leading to the activation of apoptotic enzymes.

Necrosis is characterised by the rupture of the cell membrane and loss of the intracellular contents. The necrosis death pathway has also emerged as a type of active PCD. Among these pathways, the best-characterised one is termed “necroptosis”. The activation of specific death receptors (or necrosome) such as TNF alpha receptor 1 or Toll-like receptors lead to its initiation. Other proteins are recruited until the mixed lineage kinase-like pseudokinase (MLKL) is phosphorylated and the cell membrane is broken down.

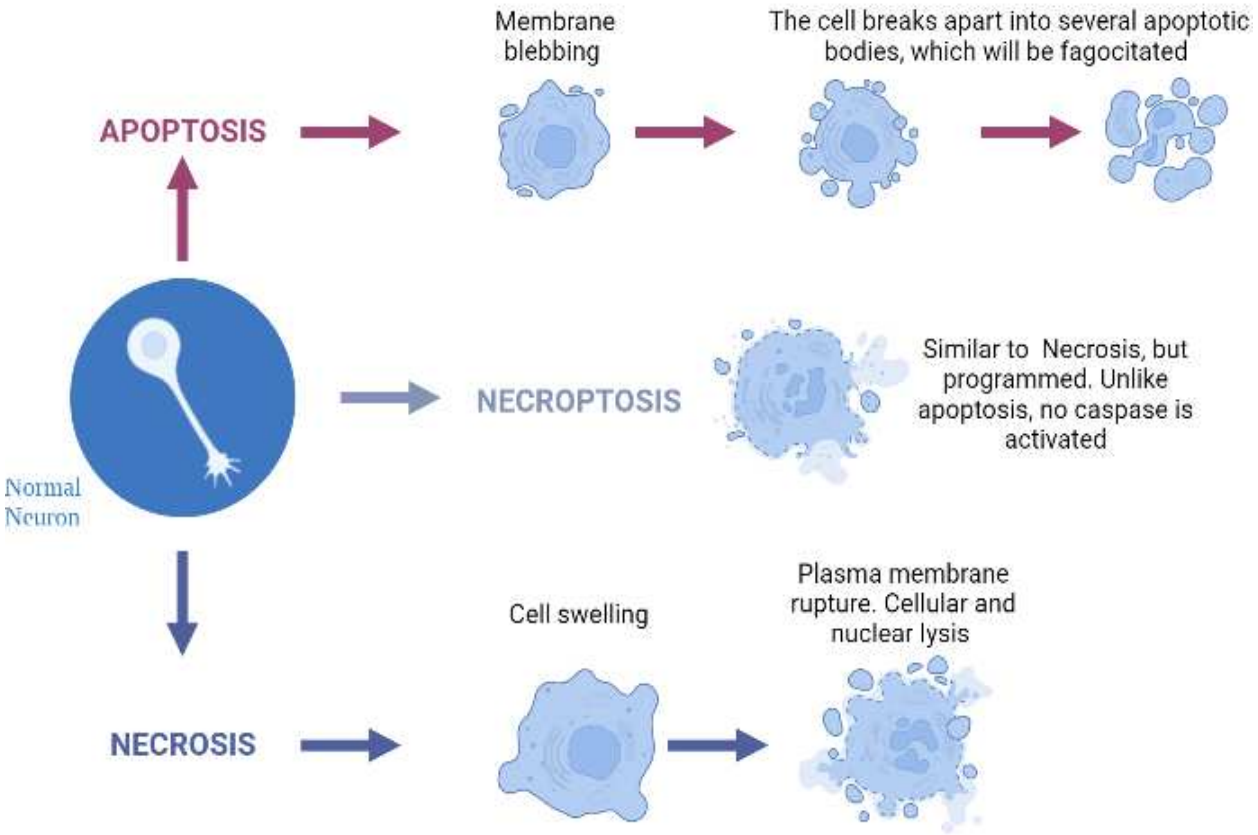

Figure 4. Mechanisms of neuron's death: Apoptosis, Necrosis and Necroptosis.
Image self-produced on Biorender.com.

(Informations for this paragraph come from Hao Chi and colleagues review "Neuronal Cell Death Mechanisms in Major Neurodegenerative Diseases")

1.2 MILD COGNITIVE IMPAIRMENT

Dementia can be preceded by a state of Minor or Mild Cognitive Impairment defined from The Alzheimer's Association as an early stage of memory loss or other cognitive ability loss in individuals who maintain the ability to independently perform most activities of daily living.

1.2.1 MCI impact

According to the report *More Than Normal Ageing: Understanding Mild Cognitive Impairment*, published in the 2022 edition of American Alzheimer's Association *Alzheimer's Disease Facts and Figures* approximately 12% to 18% of people aged 60 or older are living with MCI. An estimated 10% to 15% of individuals living with MCI develop dementia each year and one-third of the cases does it within five years. The number of people living with MCI increases with age (Alzheimers facts and figures special report 2022). However, not necessarily all the people with MCI will develop Dementia, unlike the so-called "converters" individuals.

1.2.2 MCI forms

The person affected and their relatives can notice some cognitive changes but not necessarily MCI can develop into dementia. In some cases, in fact, it can remain stable and could also revert to normal cognition.
Cognitive impairment has to be distinguished based on its forms. It can, as a matter of fact, derive also from side effects of medicines, blood vessels disorders and depression, conditions not linked to dementia (National Library of Medicine 2020). These types of MCI are part of the so called "syndromic" MCI, that is MCI for unknown reason or due to causes other than the brain changes associated with Alzheimer's disease. It differs from the term "MCI due to Alzheimer's disease" which describes MCI with the presence of Alzheimer's disease-related biomarkers.

1.2.3 MCI due to AD categories and stages

MCI, when linked to dementia, in classified by experts into two categories:

- Amnestic MCI: MCI that primarily affects memory. To give an example, one could forget appointments, conversations or recent events.
- Nonamnestic MCI: MCI that affects both thinking skills and memory, including difficulty in making sound decisions, unawareness of time or sequence of steps needed to complete a complex task.

1.2.4 Diagnosis through questionnaires

The diagnosis of MCI is best made by the personal doctor and medical care. Some cognitive tests are available and standardised to assess cognitive impairments. They can also be given to patients through time to notice potential worsening of their results.

The most common tests are:

- Montreal Cognitive Assessment (MoCA): Lasting 10 to 15 minutes, this test includes memorising a short list of words, identifying a picture of an animal, and copying a drawing of a shape or object. This test seems to be the best to find MCI. (*see Figure 5*)
- Mini-Mental State Exam (MMSE): Lasting 7 to 10 minutes, this test includes naming the current date, counting backward, and identifying everyday objects like a pencil or watch.
- Mini-Cog: Lasting 2 to 5 minutes, this test includes recalling a three-word list of objects and drawing a clock. (National Library of Medicine 2020)

All these tests aim to measure mental functions such as memory, language, and recognition of objects, via a series of questions and/or simple tasks. (National Library of Medicine 2020) No preparation is needed to be given the test. Even though these tests can diagnose if you have problems with memory and cognition, they still don’t tell you the reason (National Library of

Medicine 2020), so there is no test that can give a definitive diagnosis (Alzheimers facts and figures special report 2022). Nevertheless, they can help to find out if more tests are needed to assess a structural problem. This comprehends laboratory tests such as blood tests and imaging of the brain's structure.

Throughout an observational period, Behaviour and Psychological Symptoms of Dementia (BPSD) and mood are also examined, together with in-office neurological examination to assess nerves and reflexes' condition, movement, coordination, balance and senses. Guidelines indicate that individuals with MCI should be reevaluated every six months to determine if symptoms have progressed. (National Library of Medicine 2020)

1.2.5 Example of cognitive questionnaire

The following cognitive test is an example of Montreal Cognitive Assessment (MoCa). It comprehends rapid screening for cognitive decline deterioration. The test examines different cognitive domains including attention, executive functioning, memory, language, visuoconstructive abilities, abstraction, computation and orientation. Patients are given the instructions for each test. Total score is 30 points. Score equal to or greater than 26 is considered normal. These tests won't represent the last word to assess a cognitive impairment. To give an example, north-west italian region Piemonte guidelines will send patients with a total score less than 26 to face other neuropsychological tests. If these last are within the norm, there will be a follow-up test in 6 months time, whether if they are deficient, patients will be further sent to specialist and to UVA (Alzheimer's Valuation Unit). (Istituto Superiore di Sanità 2014)

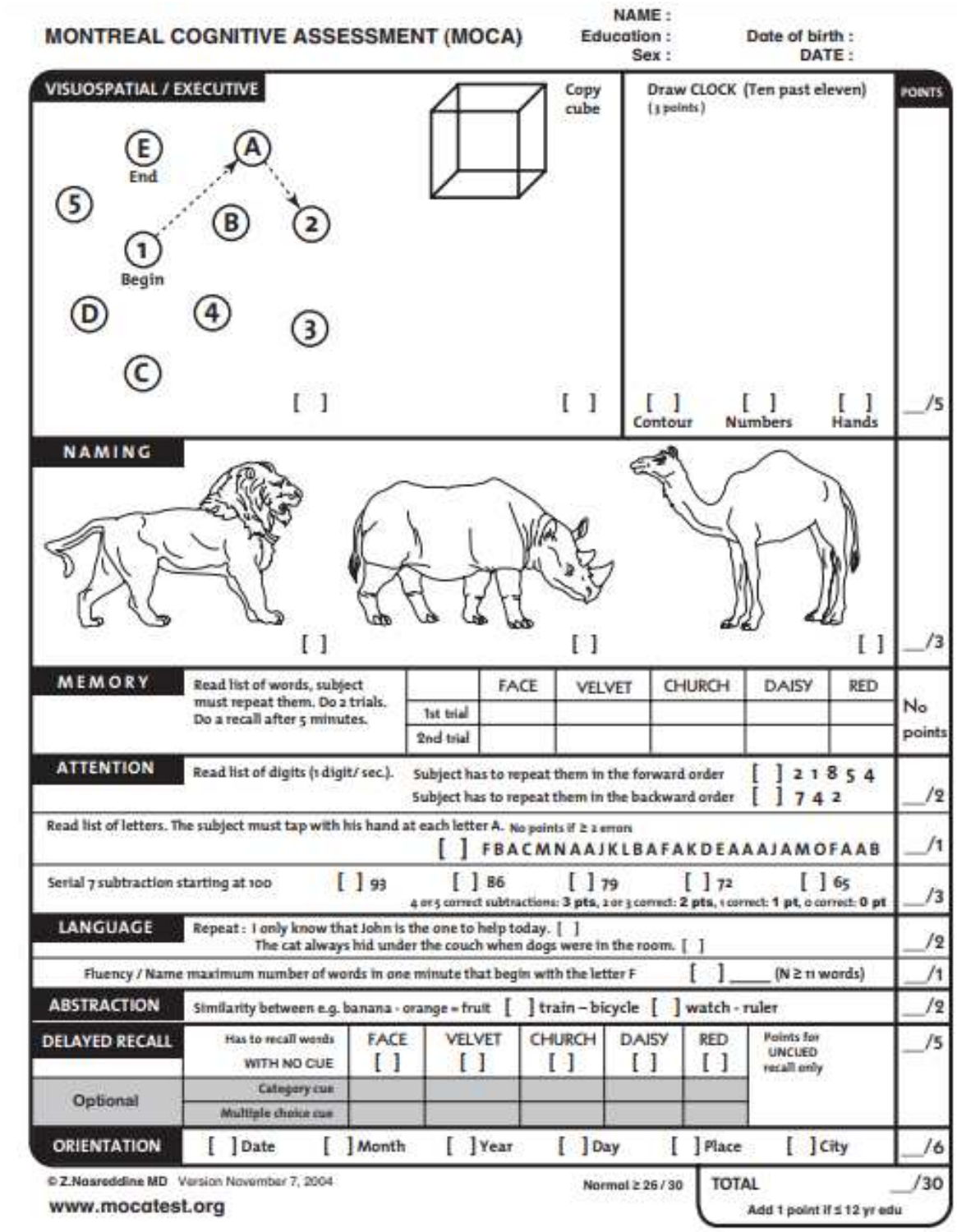

Figure 5. Montreal Cognitive Assessment (MoCa).

1.2.6 Motor disorders in dementia as tool for early diagnosis

Some types of Dementia, like Parkinson disease, have motor disorders as a feature. Alzheimer's disease is rather normally associated with cognitive functions decline even though some studies suggest that earlier motor signs are present in dementia and in some preclinical forms of cognitive deterioration too. For example, alterations of fine motor skills have been identified in individuals with MCI, together with alterations of manual dexterity and gait speed. This last seems to be a potential predictive parameter to detect cognitive decline, in particular its speed and the increasing variability of steps. Thereafter they undergo postural alterations and could find it more difficult to control their gait. Changes in facial expressions, rigidity, bradykinesia and tremor can be present too. In terms of advanced phases, some researchers found gait and balance disorders, increased muscular tone and myoclonus. In addition, apathy and sedentary behaviour of people with AD favour immobilisation, making physical decline faster. The study of Valentina Moro and colleagues reiterated that motor alterations linked to dynamic coordination and muscular tone could be advantageous indicators to direct early diagnosis. The use of Exam Geronto-Psychomoteur screening tool seems to be able to detect early motor and cognitive deficits in patients with dementia, in comparison to decline linked with physiologic ageing processes, as well as being effective to measure dementia's seriousness.

Informations for this paragraph come from Valentina Moro and colleagues work "I disturbi motori nella demenza: uno strumento per la diagnosi e l'intervento precoci." 2020

1.3 ALZHEIMER DISEASE

The most common cause of Dementia is Alzheimer Disease, approximately 60% to 75% and 80% of cases, depending on research source provenance (World Alzheimer Report 2021, Paraskevaidi 2018), even though the exact incidence is still difficult to assess.
It increases with advancing age in the sixties, exponentially rising in older people.

1.3.1 AD's stages

The scientific community agreed to describe it according to its progression (World Alzheimer Report 2021):

- Preclinical or pre-symptomatic stage which begins years in advance without any obvious symptoms.
- Mild Cognitive Impairment due to AD which includes noticeable changes in memory without affecting daily life activities. This stage could also not progress to the third stage.
- Dementia due to AD where there's solid memory loss and altered cognition and behaviour.

1.3.2 AD's symptoms

Its symptoms are sometimes difficult to notice, the most common and known feature is loss of memory which reflects initial pathology in the medial temporal lobe in the majority of cases. Other impairments can be present, but they vary in typology, usually recognized from family members before a diagnosis is made. To give an example disorientation, objects misplacement are all possible warning signs.
Early-stage AD seems associated with retinal degeneration. (Merlo 2021)
Noticeable are also BPSD that affect up to 97% of community-dwelling patients with dementia (Cloak 2023), which are changes in mood and behaviour and comprehend anxiety and agitation, sleep disorders, delirium and hallucinations, depression and even aggression.
Depression is often associated with AD and it contributes to worse clinical outcomes. (Merlo 2021)
When the pathology spreads to other brain regions, multiple cognitive domains are damaged, mobility, continence and swallowing among others. This certainly requires external support.

In case a patient reaches advanced stages of AD, it is likely that death occurs for the illness consequences and frailty, exposure to higher risk of falls, pressure sore and infections. (World Alzheimer Report 2021)

1.3.3 AD's diagnosis through questionnaires

When it comes to assessing and diagnosing dementia, the general measures of patients' cognitive abilities are evaluated by screening scales; tests are focused on problems with language, disorientation, and incorrect positioning, but may vary; the scores are then compared to the average of similar age groups and education levels. These measures are often repeated to assess whether a person is improving, stable, or declining. (World Alzheimer Report 2021)

The most famous and utilised tests are the Mini-Mental State Examination (MMSE) which tries to assess the working memory system and the Montreal Cognitive Assessment, which comprehends a series of quizzes on different functions and could be more discerning in the first phases of deterioration, like MCI.

Where possible, the complete diagnostic process will include a series of additional tests, such as basic blood tests and brain scans, and occasionally, brain scans using radioactive substances and/or a lumbar puncture to measure proteins in the cerebrospinal fluid. This latter seems to be the most relevant biological medium that can be assessed ante-mortem to analyse the conditions of neurodegenerative disorders, because of its specificity with the brain. (Checkoway 2011)

These tests, combined with accumulating information gained from observing the progression of signs and symptoms, lead to a diagnosis of the cause of AD. (World Alzheimer Report 2021)

Since neural death seems to be irreversible, strategies to find reliable biomarkers for earlier diagnosis is of utmost importance. (Merlo 2021)

1.3.4 Molecular aspects of cell dysfunction in prodromal phases of AD pathogenesis

The two main neuropathological features of Alzheimer's disease first described by German neuropathologist Alois Alzheimer in 1907 are extracellular inflammatory or neuronal senile plaques (NPs), which consist of aggregates of amino acid (A) proteins, and intracellular neurofibrillary knots (NFTs), which are formed by aggregates of tau proteins that are

associated with the onset of Alzheimer's disease, and later, with progressive loss of neurons. The mechanisms that govern the formation of NP and NFT in Alzheimer's disease are represented by the pathogenic aggregation of brain proteins. Yes believes that A and tau oligomeric soluble forms can reproduce by mechanisms similar to prion, which are the main mediators of Alzheimer's cytotoxicity.

Emerging evidence has shown that the Amyloid Precursor Protein-intracellular domain (AICD), the amyloidβ protein (Aβ), tau and Apolipoprotein E (ApoE) can all localise at the nucleus, where they modulate the transcription of key molecules involved in AD pathogenesis, as well as each other, in feedback regulatory mechanisms.
AICD regulates Aβ-degrading enzymes (neprilysin), pro-apoptotic genes (GSK-3β/β-catenin, p53, FOXO-3a) and mitochondrial genes. Aβ can enter the nucleus and directly bind DNA while the nuclear functions of tau depend upon its dephosphorylation and are implicated in protective responses against nucleic acid-damaging stressors, as well as the regulation of nuclear calcium levels and CREB activation. Moreover, Tau dysfunction at the nucleus can result in aberrant gene expression. Finally, nuclear ApoEε4 can modulate the transcription of AD-related genes in both glial and neuronal cells, including the induction of APP transcription and repression of protective SIRT1- and BDNF-encoding genes.

The glial counterpart is equally involved in disease pathogenesis, because of its possible responsibility to prevent plaque formation and cholinergic neuronal death.
Regarding astrocytes, they maintain homeostasis at many different levels, while their dysfunction affects a high number of cellular events, including neurotransmitter reuptake, metabolic support to neurons and the release of neurotrophic cues. Moreover, they are central mediators of neuroinflammation and oxidative stress, involving a wide variety of signalling pathways.

Information for this paragraph comes from Merlo et all. "Molecular Aspects of Cellular Dysfunction in Alzheimer's Disease: The Need for a Holistic View of the Early Pathogenesis. Biomolecules." 2021

1.3.5 Genetics

People carrying the gene for the production of the apolipoprotein ε4 (ApoE ε4) have a higher probability in incurring AD, being it inherited by a family member or sporadic. (Paraskevaidi 2018) Familial AD has an autosomal dominant inheritance pattern. (Checkoway 2011)
ApoE is a major cholesterol carrier and has three distinct isoforms that differ by only one or two amino acids but have very different structure and function. As explained in Maria Paraskevaidi and colleagues' Review, the human ApoE protein contains 299 amino acids, but a distinction has to be made: individuals with two alleles of ε4 have 12-fold risk to develop the disease about 10−20 years earlier than others with no ε4 alleles, whereas one ε3 allele increases the risk 3-fold. In contrast, the ε2 allele decreases the risk. (Paraskevaidi 2018) In accordance with Checkoway H. and colleagues, carriers of the ApoE ε4 allele have reduced AD ages at onset with 15-fold and 3-fold risk excesses observed in homozygotes and heterozygotes, respectively. (Checkoway 2011)
Strong evidence suggests that the major mechanism by which ApoE influences AD is via its effects on Aβ metabolism. The binding of ApoE to several cell-surface receptors to deliver lipids and in particular to amyloid-β (Aβ) peptide starts toxic events which in turn lead to synaptic dysfunction. What would normally occur is, Aβ being degraded after link with ApoE isoforms, however ApoE ε4 seems to be less effective in Aβ clearance.
Several mechanisms have been proposed for the role of ApoE in AD, such as promoting aggregation of Aβ or phosphorylation of tau. (World Alzheimer Report 2021)

Other genetic factors that increase the risk of early onset AD (i.e., below 65 years of age) include mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). APP is cleaved into fragments by α-, β- and γsecretases; proteolysis by β- and γsecretases produces a mixture of Aβ peptides: Aβ1−40 (90%) and Aβ1−42 (10%). Aβ1−42 peptides are more likely to aggregate and form amyloid plaques in AD patients. Mutations of PSEN1 and PSEN2 proteins (components of the γ-secretase) result in an increased ratio Aβ1−42/Aβ1−40. However, other studies have demonstrated contradictory results showing either decreased or unchanged levels of the proteins or impairment of the clearance rate with subsequently higher levels of the protein.

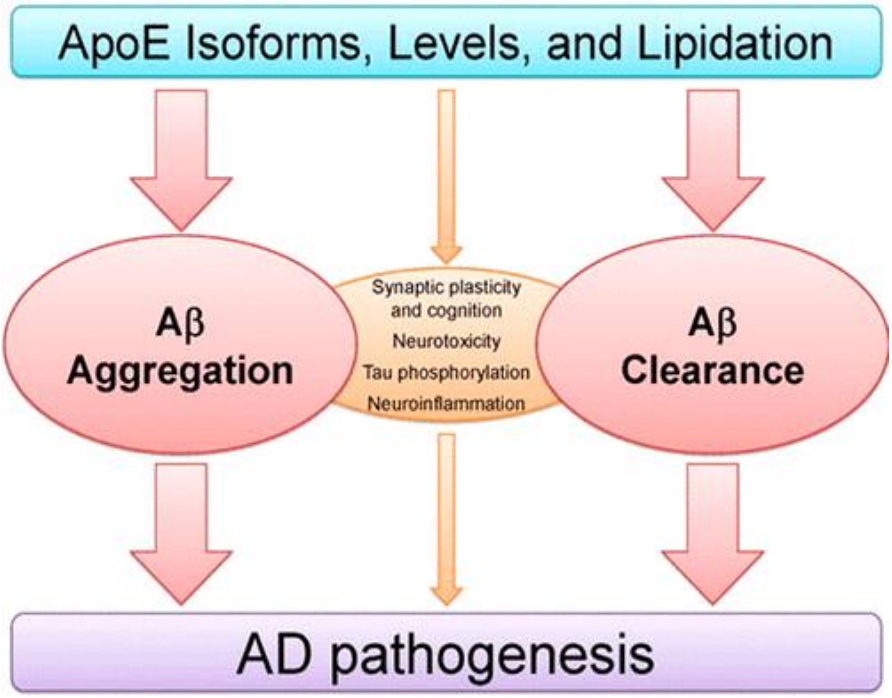

FIGURE 6. Proposed mechanisms for the role of apolipoprotein (ApoE) in AD pathogenesis.
The major effect of ApoE isoforms on AD development is via its effect on Aβ aggregation and clearance. Other mechanisms, including the effects of ApoE isoforms on synaptic function, neurotoxicity, tau phosphorylation, and neuroinflammation, may also contribute. Independent of *ApoE* genotype, differences in the ApoE levels and lipidation state may also mediate processes involved in AD pathogenesis. (Paraskevaidi 2018)

1.3.6 Pathological protein formation hypothesis

Characteristics of neurodegenerative diseases are often linked to pathological protein formation and, in many cases, high-order aggregate formation. (Chi 2018)
Despite advancing scientific research on the topic there are two main hypotheses that have prevailed:

- The amyloid cascade hypothesis, which leads to the aggregation of toxic Aβ oligomers, subsequently creating the extracellular Aβ plaques in the brain. According to Hao Chi and colleagues' review pathological evidence for the connection of Aβ deposition to neuron death is scarce.

- The tau hypothesis involves hyperphosphorylation of protein tau causing aggregation and deposits in the brain as NFTs. In a healthy brain, tau protein binds to microtubules to stabilise them with neuron cells and facilitate effective transport within the cell; in AD, however, tau protein becomes hyper-phosphorylated and detaches from the microtubules making oligomers and tangles. This is thought to induce apoptosis and this is at least part of the neurodegeneration process. (Denver 2018) The theory of tau hyperphosphorylation is not universally accepted with some suggesting that posttranslational modifications, other than phosphorylation, could promote the aggregation of tau; acetylation of tau, for instance, has been previously proposed to play a significant role in this.

Accumulating evidence suggests that Aβ plaques and neurofibrillary tau tangles are not uncommon in the brains of non-demented, cognitively healthy older people, so Aβ theory is critical, but not sufficient to explain the development of AD, which could rather derive from an altered homeostasis with plaque formation overcoming their clearance. (Denver 2018)

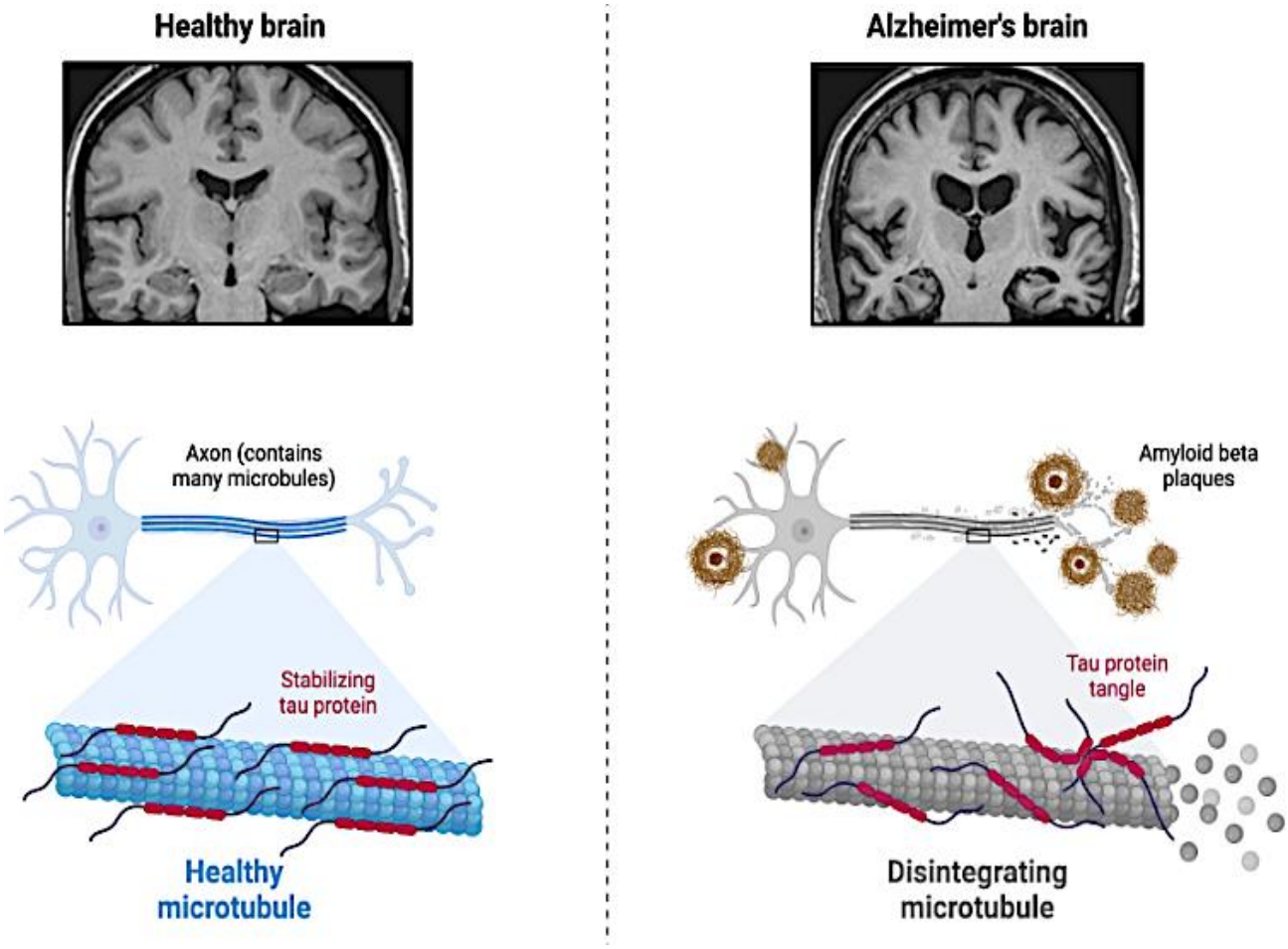

Figure 7. Difference in healthy and AD's brain axons: healthy and disintegrating microtubules.

"Pathology of Alzheimer's Disease 2", by BioRender.com

The initial sites and spread of neurofibrillary tangles within the brain are entirely predictable: they start in the allocortex of the medial temporal lobe (entorhinal cortex and hippocampus), then spread to the associative isocortex, sparing the primary sensory, motor, and visual areas until the very end stages.

Similarly, Aβ deposition is also predictable, starting in the isocortical areas of the brain, then spreading to allocortical brain regions and in the later stages to subcortical structures, including the basal ganglia and the cerebellar cortex.

Aβ is transported across the Blood Brain Barrier (BBB) into the brain by receptors for advanced glycation end products (RAGE) and transported out of the brain by low-density lipoprotein receptor-related protein 1 (LRP1). Lower levels of LRP1 expression in endothelial cells around the BBB have been reported in AD patients; inversely, RAGE levels

in endothelial cells and neurons have been shown to be elevated in AD patients, leading to accumulation of toxic protein aggregates. (Xu 2023)

1.3.7 Other mechanisms linked to neural cell death

Other potentially relevant disease mechanisms include microvascular damage, which in turn reduces blood flow and nutrients in the brain, oxidative stress, inflammation and mitochondrial dysfunction. (Checkoway 2011) Lysosomal dysfunction has also been supposed to be linked with degeneration, via mishandling of amyloid processing, and consequent defects in axonal transport, autophagy, handling of lipids, and cytoplasmic calcium overload. (Fricker 2018)
Taken altogether, the mechanisms of cell death in AD are reportedly still not clear. Understanding cell death in AD is complicated, we still don't know which stimulus initiates the onset of cell death, with scientists finding hardness in catching the exact moment of a neuron dying, considering the long time course of AD. (Fricker 2018)

1.3.8 Management of cognitive decline

Although there is a possibility of developing dementia related to genetics, epigenetics and the environment certainly increase the risk of neurodegeneration. It seems that there are no effective treatments yet, also because the brain barrier is difficult to cross and drugs are difficult to be delivered. Nanomedicine could represent a solution to this, but its strategies need to be studied in the future. (Lamptey 2022) The majority of drugs developed for AD have not achieved their primary clinical results due to their trials in mice instead of men. These experiments must face the problem of reproducing the enormous heterogeneity of the different genetic and environmental risk factors present in humans. In addition, drugs developed to dissolve A plaques do not seem to improve cognitive conditions. This is related to the question of plaques aggregates, which is still under discussion, as it is possible for them to be present in normal older brains as well. (Denver 2018)

1.3.9 Modifying risk factors to prevent Dementia

In recent years, consideration of risk factors is of utmost importance to prevent dementia, supported by yet inefficient pharmaceutical means. In this contest, the complex concept of

Exposome is born. According to Wild et al, the exposome is a complex array of environmental exposures humans encounter from birth to death that can be quantified and linked to complex phenotypic traits. Therefore, three kinds of exposures make up the exposome:

- Social environmental factors, which include education (a hypothesised factor for AD and related Dementia), financial & social status;
- Biomedical environmental factors, including environmental pollutants, lifestyle factors, and medical interventions;
- Endogenous factors, which are exemplified by metabolism, physical activity, and gut microflora. (NIA Virtual Workshop 2020)

While it is difficult to change external factors in everyday life, social and economic conditions can be restrictive, so it seems that the above-mentioned internal factors offer a higher probability of adjustment. Although nutrition sometimes moves at the same pace as economic status, due to increased choice in grocery stores for more economical fraudulent foods and dishes, there are still choices to reduce unhealthy daily exposure. To incorporate the multitude of beneficial mechanisms that promote brain health, multidomain interventions targeting several risk factors and mechanisms are likely to be the most beneficial approach, given the heterogeneity and multifactorial nature of AD. (Alanko 2022)
Among some potentially modifiable risk factors, there are vascular factors and lifestyles, including mental and social factors. Because of their adjustable nature, many of these factors provide prevention opportunities. In fact, consistent observational evidence estimates that one third of AD cases worldwide are due to seven common modifiable risk factors: diabetes, heart disease, obesity, physical inactivity, depression, smoking and low education. Multi-area interventions are already successfully used to prevent cardiovascular disease and diabetes, and targeting these multi-area interventions to patients at higher risk of dementia appears to be an effective strategy. Furthermore, compliance with lifestyle changes is an important problem in enhancing the effectiveness of any intervention that has advantages beyond dementia prevention. In fact, multi-faceted interventions to treat risk factors related to vascular and lifestyle in older adults are likely to have a positive impact not only on perception, but also on the prevention of other chronic diseases and disabilities. Not to mention improvements in self-computing and general health and reduced risk of new chronic diseases. (Kivipelto 2018)

2. MUSCLE BRAIN AXIS

2.1 Muscle-brain axis

When claiming the beneficial effects of exercise, we indirectly consider the existence of a crosstalk between the muscles and the brain, which we can call the “muscular brain axis”. This term aims to explain how muscle is used as an endocrine organ to affect cognitive and neuronal function. According to the literature, a large network of brain regions, equivalent to 82% of the total volume of grey matter, seems to be modulable by physical activity. (Pedersen 2019) This means different and complex pathways that are not yet fully understood. Physical exercise increases cognitive function and brain health by increasing brain volume or connectivity: neuronal and vascular adaptation promotes neurogenesis and synaptic plasticity, angiogenesis and metabolism change. These positive effects are mediated by various factors, including trophic factors, changes in genes' expression levels, reductions in inflammation and proinflammatory processes, and improvements in brain redox status. On the other hand, people with low muscle mass may be affected by insulin and protein metabolism, mitochondrial functions beyond systemic inflammation, which contributes to cognitive disabilities. (Oudbier 2022) Another path is the positive effects of exercise and the positive correlation between muscles and the human intestinal microbe. (Schlegel 2019)

2.1.1 Physical exercise

Physical activity (PA) can be defined as every human body movement produced by the skeletal muscle which requires greater energy expenditure compared to that at rest. This term comprehends both sport disciplines and recreational exercise in leisure time, as well as active work done for job and other activities of daily living.
Physical activity’s quantification can be realised with the Metabolic Equivalent of Task (MET), which represents the ratio between energy’s consumption during a muscular task and energy’s consumption at rest. This ratio corresponds to 3,5 ml O_2/kg body weight/min. An intensity classification based on METs would look like:

- Light PA: under 3 MET, e.g. while slowly deambulating (<4km/h).
- Moderate PA: 3-6 MET, e.g. while deambulating at 4-7 km/h.

- Intense PA: over 6 MET, e.g. while deambulating at more than 7 km/h.

With the term Physical Exercise instead, we refer specifically to a form of physical activity which is intentional and characterised by planned, structured and repetitive human body movements, which aims at improving and/or maintaining one or more physical fitness components, that in turn bring improvements and/or conservation of one's health status. Components on the list are, for example, cardiorespiratory fitness, muscular Fitness, body composition, flexibility and neuromuscular fitness.

Information for this paragraph comes from the first chapter of the book "L'uomo e il movimento, lineamenti di teoria e metodologia" by Casolo A. 2020

2.1.2 Hypokinesia and sedentary lifestyle issue

Sedentary lifestyles are increasing worldwide, because of environments that promote technology and poor active work, urbanisation and automobile-focused community design. Besides that, opportunities for real life social relationships diminish, which may also contribute to inactivity.
With opportunities for physical activity continuing to decline, major negative health, social and economic consequences appear.
This led organisations and experts to write the so-called "Toronto Charter " which tries to give open access guidelines for all countries, regions and communities to strive for greater political and social commitment to support enhancement of physical activity. According to this document physical inactivity is the fourth leading cause of chronic disease mortality such as heart disease, stroke, diabetes, cancers; it also contributes to the increasing level of childhood and adult obesity. At this point, it is clear how much physical inactivity contributes substantially to direct and indirect health care costs and has a significant impact on productivity and healthy life-years.
Moreover COVID-19 pandemic seems to have worsened the situation. According to data from the last European investigation in 2022, 45% of questioned people declared not to exercise or do sport and it's estimated that this behaviour leads to the onset of millions of non-communicable chronic diseases cases. (Epicentro 2023) People also reported a decrease of physical activity due to restrictions and confinement. Increasing levels of physical activity could therefore help with COVID-19 recovery by creating a healthier, more resilient population, improving mental health and social connection. (OECD 2023)

According to the World Health Organization more than a quarter of the world's population are insufficiently active (around 1 to 3 women and 1 in 4 men), with insufficient activity increasing by 5% in high-income countries between 2001 and 2016, according to their health recommendations parameters. The Organization explains this drop with inaction during leisure time and sedentary behaviour on the job and at home, as well as the use of means of transport. Inactivity among adolescents is of great concern: globally, 81% of adolescents aged 11-17 years were insufficiently physically active in 2016, that means they didn't reach the amount of 7 hours of moderate to vigorous intensity physical activity in a week. (WHO 2023)

2.1.3 WHO recommendations

Recommendation of the World Health Organisation is practising 150 minutes of moderate-intensity physical activity per week. This could:

- Prevent more than 10000 premature (people aged 30 to 70 years) death per year;
- Increase overall life expectancy;
- Save European Member States 0.6% of their health care budget on average.

WHO took care of listing recommendations based on different ages: adults are exhorted to do at least 150-300 minutes of moderate-intensity (or 75-150 of vigorous-intensity or a combination of moderate and vigorous intensity) aerobic physical activity per week, together with muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week. Clearly, nothing prohibits doing more. They also encourage to replace any sedentary time with any form of physical activity.
WHO then differentiates adult people above 65 years old from people below that age, inciting them to do varied multicomponent physical activity that emphasises functional balance and strength training at moderate or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls.
This also applies to people living with chronic conditions like hypertension or type 2 diabetes and for adults living with disabilities for whom they suggest avoiding sedentary behaviour and be physically active while sitting or lying like doing upper body led activities, inclusive and/or wheelchair-specific sport and activities.

Information for this paragraph comes from WHO guidelines, 2023

2.1.4 PA benefits for health outcomes

Regular physical activity has numerous health and well-being beneficial effects.
It reduces all-cause mortality, as well as the risk of coronary heart disease, high blood pressure, stroke, insulin resistance, type 2 diabetes, some types of cancer, depression, anxiety, neuro-degenerative diseases and falls. Other benefits include increased cardiorespiratory and muscular fitness, enhanced immune system, healthier body mass and composition, improved bone health, increased functional health, improved cognitive function and better sleep.
Concerning older adults, PA reduces risk of fall-related injuries, preserving physical function and mobility and delaying the onset of major disabilities. It also functions as a protective mechanism for depressive symptoms across all ages. (OECD/WHO 2023)
Furthermore, recent WHO guidance in risk reduction of cognitive decline and dementia states that physical activity should be recommended to adults with normal cognition (strong recommendation) and those with mild cognitive impairment (conditional recommendation) to reduce the risk of cognitive decline.
In fact, greater amounts of moderate- to vigorous-intensity physical activity are associated with improvements in cognition (e.g. processing speed, memory, and executive function), brain function and structure, and a reduced risk of developing cognitive impairment, including Alzheimer's disease. (WHO 2023)

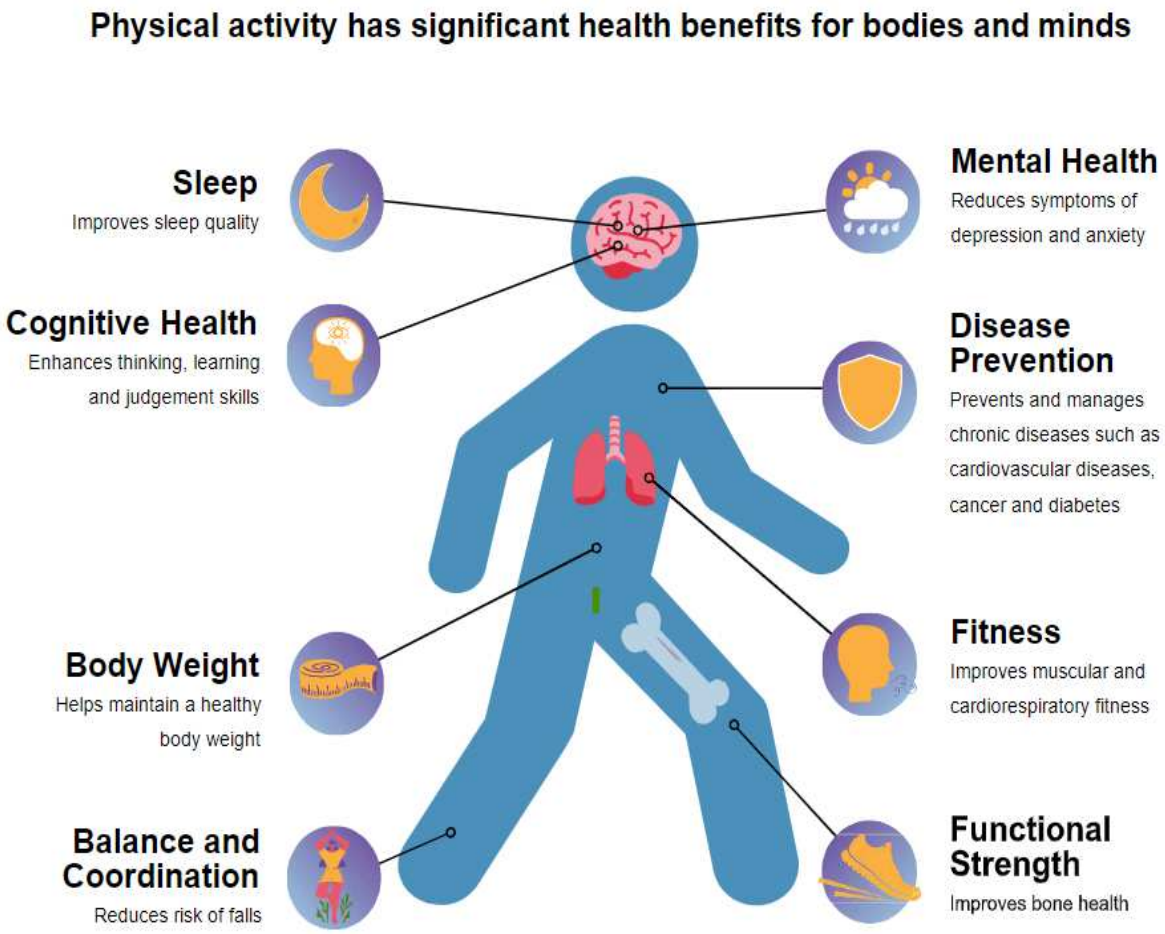

Figure 8. The health benefits of physical activity.

Infographic comes from *Step Up! Tackling the Burden of Insufficient Physical Activity in Europe,* OECD Publishing

2.2 MUSCLE-BRAIN AXIS COMPONENTS

2.2.1 Vascular hypothesis and Physical activity preventive influence

With the income of Atherosclerosis, an individual is three times more likely to develop AD. This disease leads to increased vessel stiffness, internal thickness, and inhibited vascular tone. Overtime atherosclerotic carotid and cerebral arteries attenuate cerebral blood flow (CBF) and cerebral perfusion, leading to hypoperfusion and hypometabolism. Moreover, it could accelerate amyloid-β accumulation and deposition inside and around the cerebral arteries (cerebral amyloid angiopathy) which is associated with worsening of some cognitive functions as memory in older individuals. Clearing of A-β plaques is attenuated because of scarce elasticity dependent arterial pulsation. (Marston 2019)
It has been proposed that the risk of cognitive decline and dementia are reduced as a result of the protective influence that physical activity has on reducing vascular dysfunction and risk factors. As Kennedy and colleagues explain, during exercise the heart rate is increased; however, as a result of chronic exercise the heart rate remains lower at rest reducing the overall number of cardiac cycles and the degree of pulsatile stress on arteries. One study demonstrated that middle-aged adults who regularly engaged in moderate to vigorous aerobic exercise had lower stiffness of the central arteries when compared to a sedentary cohort. Moreover, both aerobic and resistance exercise improve endothelial function, with aerobic exercise being the most effective with dose-response relationship. (Kennedy 2017)
Marston and colleagues claim that while it is unlikely that resistance training protects against vascular dysfunction through alteration in arterial compliance, there is evidence supporting the positive impact of resistance training on adipokines, such as adiponectin which enhances vasodilation. (Marston 2019)

2.2.2 The importance of well-functioning insulin metabolism

As Oudbier and colleagues suggest, insulin resistance, which is associated with low skeletal muscle mass, is an independent risk factor for cognitive decline. (Oudbier 2022)
Insulin is also an important neuromodulator which affects both synaptic and postsynaptic activity, particularly through its ability to modulate signalling by potentiating receptors that

play important roles in synaptic plasticity, learning, and memory, like GABA receptors. (Kenndey 2017)

Brain tissue metabolism mainly depends on glucose; when this monosaccharide is strongly present in peripheral tissues, normal regulation is hindered and this goes to the detriment of brain insulin sensitivity. Chronic hyperinsulinemia, originating from long-term exposure to elevated concentration of glucose, dampens tissue sensitivity to insulin, leading to cerebrovascular damage. In fact, both utilisation and uptake of glucose are impaired in individuals with AD. Interestingly, AD patients have defects in hippocampal glucose metabolism prior to clinical manifestation. (Xu 2023) Peripheral insulin resistance and so, hyperinsulinemia, affects this molecule's signalling in the central nervous system which in turn stimulates tau phosphorylation, oxidative stress, and toxicity of Aβ.

A sedentary lifestyle is very likely to be a crucial aspect in the ever-increasing incidence of insulin resistance in the population. Aerobic exercise, at least long-term, regular, intensive exercise, was shown to prevent the reduction in insulin sensitivity associated with increasing age together with improved cognitive outcomes for those with MCI or early dementia (Kennedy 2017).

Mann et al. systematically reviewed the responses of insulin sensitivity to different modalities of exercise. They concluded that both aerobic exercise and resistance training were effective in improving insulin sensitivity, and that combining the two was the most efficient strategy (Kennedy 2017)

Information for this paragraph comes from Oudbier and colleagues' review "Pathophysiological Mechanisms Explaining the Association Between Low Skeletal Muscle Mass and Cognitive Function" 2022

2.2.3 Mitochondria neuroprotective role

Being physically active allows one to maintain mitochondrial integrity and structure, as well as mitochondrial functions, which are a multitude and can affect cells in different ways. These organelles are mainly localised in neuronal axons and dendrites and are responsible for ATP generation, for maintaining electrochemical neurotransmission and for cell repair. (Castelli 2019)

It is unclear whether mitochondrial dysfunction is a cause or consequence of neurodegenerative diseases, it certainly is a determining factor of their progression. The brain

has high energy requirements and mostly relies on oxidative energy metabolism, depending on continuous adequate oxygen and substrate supplies. What provides energy to the brain is mitochondrial oxidative phosphorylation consisting of the electron transport chain, which complexes can be linked to neurodegeneration if dysfunctional. It has to be specified that mitochondrial dysfunctions are various between individuals within specific neurodegenerative disease categories. (Burtscher 2021) To give an example, pathological tau seems to have a direct impact on mitochondria, inducing neuronal bioenergetic damage and leading to cognitive impairment in AD. (Xu 2023)

Talking about aerobic metabolism, moderate reactive oxygen species (ROS) formation is a regular occurrence. Nevertheless, they can lead to oxidative stress when there is an imbalance between oxidants and antioxidants in favour of the former. ROS production can be aggravated by mitochondrial damage. High ROS levels in mitochondria can lead to damage of DNA, lipids and proteins impairing maintenance of membrane potential, trans-membrane transport, proteostasis, and enzyme activities. Oxidative stress seems to be an early pathological process in AD. (Burtscher 2021)

Beyond their pivotal role in cellular energy metabolism production, mitochondria are also involved in cellular Ca2+ homeostasis and nuclear gene transcription regulation. In fact, altered Ca2+ signalling is involved in impaired cognition. In the aged brain, with possible mitochondrial damage, a failure in the normal antioxidant defence mechanisms occurs, which renders the brain more vulnerable to the lethal consequences of oxidative stress. (Castelli 2019)

Moreover, ageing causes the immune system's decline because of the increase in proinflammatory cytokines resulting in a chronic low inflammatory state. This increases levels of mitochondrial dysfunction which in turn leads to metabolic abnormalities like insulin resistance and muscle degradation via the activation of the ubiquitin–proteasome system. (Oudbier 2022)

Deficits of mitochondrial biogenesis have been shown for some neurodegenerative diseases, among which AD and PD. The term "mitochondrial biogenesis" describes the increase of mitochondrial mass from pre-existing mitochondria. It is controlled by numerous pathways like that of the cotranscriptional factor peroxisome-proliferator-activated receptor γ coactivator-1α (PGC-1α) which can be induced with exercise by AMP-activated protein kinase (AMPK). As we age, responsiveness of AMPK signalling diminishes and could lead us to be more vulnerable to neurodegenerative disease, not only for its effects on mitochondrial biogenesis but also for its modulatory role in inflammatory responses,

antioxidative defences, and autophagy. The metabolic pathway of PGC-1α indirectly also promotes BDNF expression. (Castelli 2019) The efficient clearance of dysfunctional mitochondria is crucial for cell survival as well; impaired mitophagy has, for example, been demonstrated in models of AD. (Burtscher 2021)

Apart from change in mitochondrial mass (as in biogenesis and mitophagy), what can vary and modify the organelles' function are morphological variations, like fusion, which facilitates oxidative phosphorylation and the inter-mitochondrial exchange of metabolites and mitochondrial DNA and fission which enables more efficient mitophagy. Alterations of mitochondrial dynamics are suspected to be involved in the neurodegenerative process and have been demonstrated in models for all major neurodegenerative diseases, including AD. Alzheimer's disease seems to be associated with missense mutations in proteins involved in mitochondrial dynamics.

Mitochondria not only release and react to signalling molecules, but they can also be transferred between cells as whole organelles or organelle components. It has not been confirmed yet, but the role of mitochondrial transfer in exercise signalling in general, and specifically to the brain, is a topic of interest. Mitochondria can in fact also be transferred between different cell types as whole organelles or organelle components. This includes, for example, the exchange of mitochondria between astrocytes and neurons to assist with the degradation of damaged neuronal mitochondria, which has resulted in beneficial outcomes for brain tissues. (Burtscher 2021)

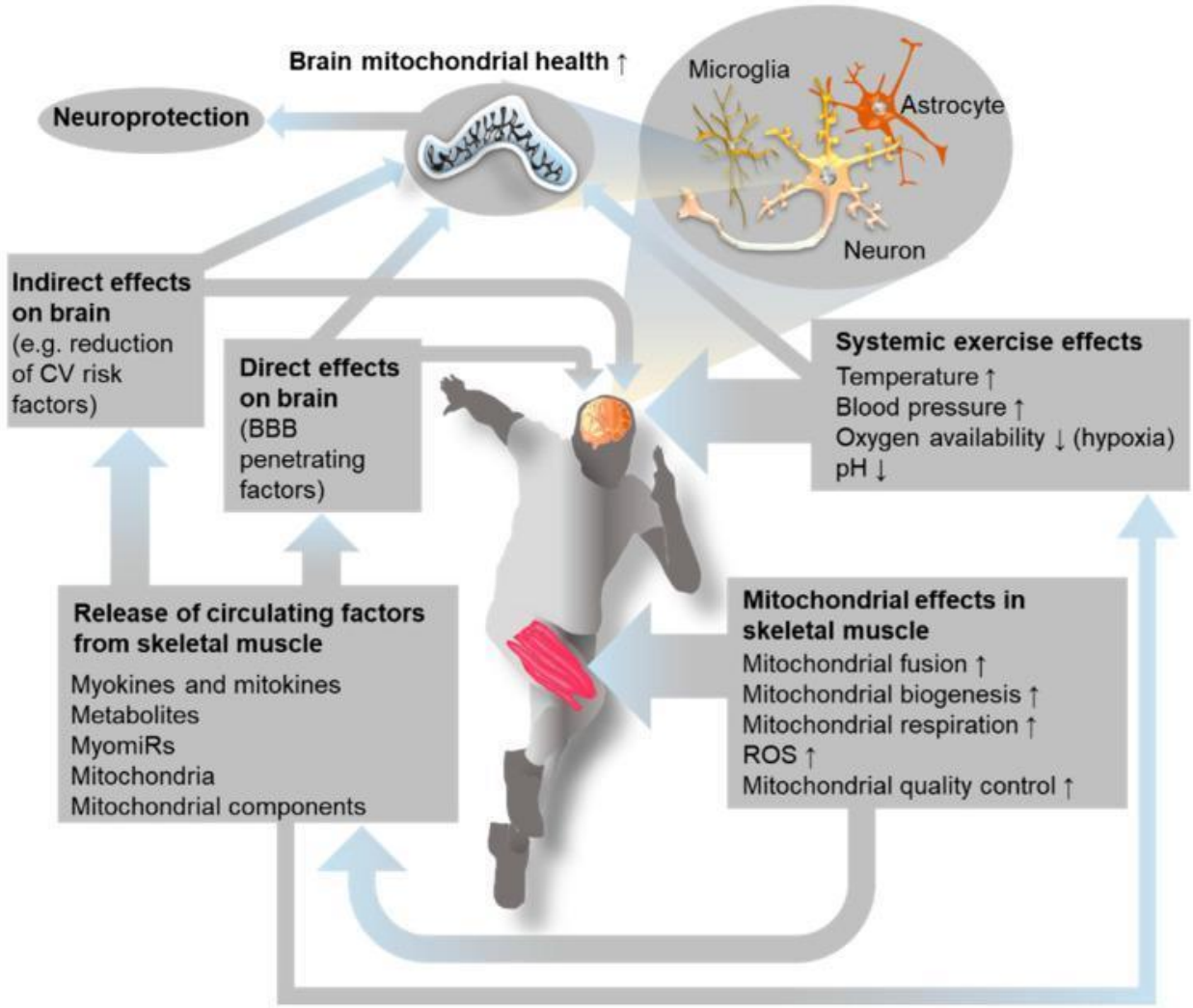

Figure 9. Factors controlling exercise-induced communication from muscle to brain: the central role of mitochondria.

CV=cardiovascular; BBB= blood–brain barrier; ROS= reactive oxygen species; MyomiRs=microRNAs released from muscle

Infographic comes from Burtscher, J.; Millet, G.P.; Place, N.; Kayser, B.; Zanou, N. The Muscle-Brain Axis and Neurodegenerative Diseases: The Key Role of Mitochondria in Exercise-Induced Neuroprotection. 2021

2.2.4 Exercise and Liver-Brain axis

B-hydroxybutyrate, a ketone body produced in the liver and released in the bloodstream through Physical exercise's induction, was previously recognised for its ability to confer neuroprotection in Alzheimer's, Huntington's and Parkinson's disease. Specifically, β-HB can cross the BBB and increase BDNF transcription through the activation of BDNF promoters.
In addition to β-HB, the liver has been shown to release the hepatokine, fibroblast growth factor 21 (FGF21), in response to exercise.
Finally, Insulin-like growth factor-1 (IGF-1) may also be a key player within the liver-brain axis in response to exercise. IGF-1 is produced by several tissues, including the skeletal muscle and liver, with the latter being the main source of IGF-1 that is released into the body. In response to exercise, circulating IGF-1 has been shown to infiltrate the brain through the blood cerebrospinal fluid pathway, resulting in an increase in the number of new neurons, especially in the hippocampus.

Information for this paragraph comes from Nay and colleagues review "Molecular Mechanisms Underlying the Beneficial Effects of Exercise on Brain Function and Neurological Disorders" 2021

2.2.5 Exercise and the Microbiome–Gut–Brain Axis

Human body microbiome is the community of living microorganisms that live with our organisms without being harmful. Especially in our gut, they form an entire ecosystem which results in being capable of communicating with other organs.
Gut microbes are able to communicate with the CNS, forming a microbiome–gut–brain axis too.
Good levels of fitness are correlated with greater variety of microbiome and interestingly, physical exercise-induced behavioural and mental health improvements are associated with the alteration of specific strains of bacteria within the gut.
Hypothesis for ways of communication between muscle and microbiota in response to exercise are the following:

- Activation of Vagus Nerve, which is the only cranial nerve linked to the gut. There is, however, a lack of empirical evidence for this hypothesis.
- Exercise's impact and regulation on hypothalamic–pituitary–adrenal axis, via modulation of gut microbiota.
- A minor fraction of colon-derived Short-chain fatty acids (SCFAs) can cross the BBB and have neuroactive properties, among which integrity of BBB itself and controlled passage of molecules and nutrients from the circulation to the brain. In this way the brain can properly develop, and CNS homeostasis can be protected. Exercise can increase SCFAs, in particular butyrate, which mechanistically reduces gut permeability by augmenting mucus production and modulating synthesis of tight-junction proteins.

  Interestingly, exercise is associated with a greater abundance of commensal bacterias that reduce intestinal permeability, limiting the release of lipopolysaccharides from Gram-negative bacteria and consequent systemic increases in inflammatory markers.
- Gut microbiota play a role in neurotransmitter metabolism, particularly of serotonin and tryptophan. When released into the bloodstream, they have positive effects on mood state.

Even if this information opens many doors for understanding of the gut-brain axis, further research is required to better understand if and how exercise influences the microbiome.

When microbial dysbiosis (MD) occurs, the gut barrier is altered and bacterias are translocated in the bloodstream. The study of Giacconi and colleagues reported that blood bacterial DNA levels are higher in MCI and AD patients compared to elderly controls, therefore these high levels may promote peripheral- and neuro-inflammation, contributing to cognitive impairment. This agrees with findings of extracellular bacterial DNA promoting Tau misfolding and β-Amyloid.
MD also influences brain-derived neurotrophic factor (BDNF) production, whose alterations contribute to the etiopathogenesis of Alzheimer's disease (AD). Bacterial brain infection stimulates the synthesis of cerebral BDNF which is considered to be a neuroprotective response against harmful stimuli. (Giacconi 2023)

Information for this paragraph comes from Nay and colleagues review "Molecular Mechanisms Underlying the Beneficial Effects of Exercise on Brain Function and Neurological Disorders" 2021

2.2.6 Metabolites of the Muscle–Brain Axis

Skeletal muscle secrets metabolites in response to exercise which could play a role in this muscle crosstalk we're examining. Among them the Lactate has been found and investigated: it is an end-product metabolite of glycolysis when there's insufficiency of cells oxygen availability and it accumulates in skeletal muscle in response to contraction. This molecule can serve also as an energy substrate for skeletal muscle cells and other tissue like the heart and brain. In the context of exercise, lactate can accumulate in the blood depending on the intensity and duration of the exercise stimulus, can cross the BBB and reach neurons. Increases in peripheral blood lactate levels at rest in humans have been associated with an increase in circulating BDNF even if the underlying mechanisms have only been hypothesised, as lactate could activate the PGC1α/FNDC5 pathway, which in turn promotes BDNF expression, thus enhancing memory and learning. (Nay 2021)
Lactate also acts at central level influencing neuronal activity, calcium signalling, axonal myelination, angiogenesis and memory formation.
Prolonged exercise diminishes brain glycogen essentially stored in astrocytes providing lactate to adjacent neurons. This lactate shuttle from astrocytes to neurons has been implicated in long-term memory formation and has been shown to influence endurance capacity. (Delezie 2018)

2.2.7 Circadian muscle secretome

A group of neurons called Suprachiasmatic Nucleus (SCN) located in the hypothalamus is in charge of controlling hormonal and functional fluctuations in mammals. This phenomenon is also known as Circadian Clock and destruction of these neurons leads to impairment of the normal sleep-wake rhythm. Through information coming from ganglion retinal cells via retinohypothalamic projection the SCN receives information about day length to send them to the pineal gland which can then produce melatonin. Intracellular circadian clock is based on interconnected molecular loops with triggers and repressors.
Circadian clocks also control processes such as gene regulation, protein synthesis and export, enzyme activity, cell signalling, nutrient accumulation, on a 24-h time scale. When irregular sleep-wake cycles or meal timing chronically disrupts circadian rhythms, there is a higher

association with obesity and other metabolic conditions, cancer and inflammation, sleep as well as cognitive and mental disorders.
In skeletal muscle, the molecular clock has been linked to cell growth and repair, autophagy, insulin sensitivity, lipid homeostasis, mitochondrial metabolism and respiration. Moreover, scheduled exercise is a potent stimulus to regulate circadian timing in skeletal muscle. Interestingly, human primary myotubes harbour a cell-autonomous circadian clock involved in the basal release of cytokines (e.g., IL-6, IL-8) and other proteins. It is likely that a transcriptional regulatory network, involving circadian nuclear receptors and the coactivator protein PGC-1α coordinates the time-of-day dependent accumulation of myokines in muscle cells and secretion into the circulation. Although more research is needed, it is easy to understand how there can certainly be time windows during which exercise can exert maximal effects on brain physiology.

Information for this paragraph comes from Delezie and Handschin review "Endocrine Crosstalk Between Skeletal Muscle and the Brain" 2018

2.2.8 Fighting sarcopenia: a step in the prevention of Cognitive decline

Sarcopenia is described as a condition of progressive degeneration of muscle mass and function, which leads to increased frailty and functional decline. (Scisciola 2021, Oudbier 2022) Reduction in general activities in advanced age has been indicated as a main contributor to the onset of sarcopenia. (Arosio 2023)
This has also detrimental effects on cognitive function. In fact, the prevalence of sarcopenia in older individuals with dementia is three times higher than other peer individuals. In these individuals, the release of myokines is altered, together with insulin and protein metabolism, mitochondrial function and systemic inflammation, which we already discussed in the previous sections.
Skeletal muscle mass loss that occurs with ageing is explainable by the decline of immune function, the occurrence of anabolic resistance (reduction and suppression of protein synthesis) and increase in ROS production. (Oudbier 2022)
The question whether changes in neuromuscular junctions (NMJs), the direct link between the nervous system and muscle, can trigger or follow sarcopenia is still not completely understood. NMJ deterioration and an imbalance in PI3K–AKT–mTOR axis may act synergistically to induce age-related muscle decline. (Arosio 2023) Here is another pathway

through which physical activity and exercise can reveal their function, as our skeletal-muscle fitness is associated with lower risk of incurring the sarcopenic condition. (Casolo 2020)

2.3 MYOKINES

As mentioned above, muscles can be seen as an effective endocrine organ in communication with other parts and parts of the human body. In fact, it produces and releases small proteins during proliferation, differentiation, or contraction. They are defined as “Myokines” and they can have an effect on self, paracrine or endocrine regulation. Some myokines are involved in energy supply during acute exercise, and some are probably involved in mediating adaptation to training in various organs, such as the liver, intestines, pancreas, fat tissue, bone, vascular floor, skin, and brain. They also play an important role in controlling systemic glucose homeostasis, lipid metabolism, improving insulin sensitivity, and triggering white adipose tissue browning. (Scisciola 2021) At rest, they participate in regulating muscle proliferation, differentiation and regeneration. (Pedersen 2019) Inactive muscles appear to suppress their endocrine functions, leading to inflammation and thus increasing the risk of dementia. (Oudbier 2022) This suggests exercising and/or approaching an active lifestyle, so that muscles maintain their beneficial effects on the whole organism.

2.3.1 Myostatin group

Myostatin (MSTN) belongs to the transforming growth factor beta superfamily (TGF-ß). Contrary to the others, this myokine is reduced by exercise and its function is to limit muscle growth during embryogenetic development, even though it is also expressed in adulthood. It exerts its activity in its unbound form (Domin 2021).
In response to exercise, MSTN binds to the cell membrane receptors initiating the microtubule-associated protein kinase (MAPK) cascade (Domin 2021). It activates the FOXO system and inactivates mTOR while activating AMPK pathways which inhibit protein synthesis. High levels of Myostatin inhibit the satellite cell proliferation and differentiation and block the action of muscle fibre protein accretion. A positive correlation between obesity, insulin-resistance and high levels of Myostatin has also been observed. Bearing in mind that these are neurodegenerative diseases risk factors, the effects of exercise on myostatin could support the side of prevention.

Decorin, in turn, suppresses the Myostatin-effect by binding this myokine, therefore it promotes hypertrophy and regulates muscle growth upon physical exercise. It binds to multiple cell surface receptors, modulates tumour suppression, stimulates autophagy and inflammation, and inhibits angiogenesis and tumorigenesis. (Domin 2021)
Decorin-overexpression could enhance the proliferation of myoblasts and lead myotubes to grow. (Zunner 2022)

Follistatin (FST) is another important antagonist of Myostatin, which cannot only bind Myostatin, but also blocks Myostatin receptors. FST is also considered to be a hepatokine. (Sabaratnam 2022) It is regulated by the glucagon-to-insulin ratio in response to exercise (Domin 2021)
Concerning the muscular system, Follistatin can induce the proliferation of satellite cells, leading to protein synthesis. This myokine was found to have beneficial effects on systemic metabolism too. (Sabaratnam 2022) Several studies of healthy and obese individuals have shown that circulating FST levels are increased in response to acute exercise and remain elevated in the recovery period (up to 6 hours), even though hyperglycaemia and correlated factors seem to blunt FST exercise-induced release. In the elderly, it was proposed that strength training improves physical performance and muscle quality via follistatin, which blocks muscle degradation pathways, rather than via muscle growth metabolic pathways. (Hofmann 2016)

Information for this paragraph comes from Zunner and colleagues' narrative review "Myokines and Resistance Training" 2022

2.3.2 BDNF

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, growth factors that also belongs to the myokines group. (Jiang 2018)
BDNF is produced by a wide spectrum of cells, including skeletal muscle cells, cardiac myocytes, smooth muscle cells, cells in the liver and cells in the brain.
BDNF seems to have auto- and paracrine functions. It cannot pass the BBB, this renders it difficult to develop BDNF associated therapeutics for the treatment of neuronal diseases. (Zunner 2022) Exogenous administration of this molecule could not ameliorate cognitive function.

Within the neurotrophin family, BDNF exhibits the highest level of expression within the brain, where it binds to its primary receptor, tropomyosin receptor kinase B (TrkB), forming a BDNF-TrkB complex that becomes internalised and activates a plethora of signalling events involved in neuronal function. An alteration of this BDNF-TrkB signalling with ageing or pathological conditions is a potential mechanism of cognitive decline.
High levels of BDNF in the brain are associated with improvements in memory and recollection, and the restraint of cognitive decline. Conversely, decreased levels of BDNF are associated with a deterioration in memory function, neurodegeneration and cognitive impairments related also to AD. (Nay 2021)
As a neurotrophin, it is involved in the differentiation of neurons, synaptic plasticity and neurogenesis in the amygdala, prefrontal cortex and hippocampus. It is also engaged in the endogenous restoration of myocardial and skeletal muscle cells. (Zunner 2022)
Moreover, a higher expression of BDNF affects the levels of dopamine, serotonin, and melatonin in several brain regions, preventing many of the symptoms observed in individuals with depression and directly favouring learning and memory via the dopamine pathways. (Trettel 2023)
At the Neuromuscular junction, BDNF plays a central role in motor neuron viability, enhancement of AcetylCholine (ACh) presynaptic release, and postsynaptic maintenance. It is secreted as pro-BDNF by both motor neurons and myofibers and is cleaved by extracellular metalloproteases and the tissue-type plasminogen activator (tPA)/plasmin system into its mature form. The precursor seems to negatively affect synaptic transmission, while the mature form potentiates it through binding with Trk receptors expressed both by motor neurons and skeletal myocytes. Their downstream signalling leads to the activation of Phosphoinositide 3-kinase (PI3K), Mitogen-Activated Protein Kinase (MAPK) and Extracellular signal-Regulated Kinase (ERK), and phospholipase C-γ (PLCγ) pathways, ultimately supporting neuronal survival (Arosio 2023) and affecting synaptic plasticity.
BDNF, which increases growth and proliferation of hippocampal dentate gyrus cells, is involved in neuronal differentiation, plasticity, cell survival, hippocampal function, showing a dominant role in mediating the effects of physical activity on cognitive changes. Exercise-induced BDNF was shown to decrease the production of toxic amyloid β peptides, which could be important in treating Alzheimer's disease (AD).
Patients with neurodegenerative diseases, like AD, Parkinson's disease, and depression, presented low serum levels of BDNF. (Scisciola 2021) Conversely, inhibition of BDNF action in the central nervous system results in a reduction of the recruitment of CREB to

target sites on genes that mediate the exercise-induced enhancement in learning and memory. (Delezie 2018)

Different studies confirm that BDNF plasma levels are raised because of physical activity, regardless of the type of exercise (aerobic training, Tai Chi, combination of physical and mental training). Nevertheless Venegas-Sanabria affirms that resistance exercise seems to have less effect on BDNF levels compared to aerobic training. (Venegas-Sanabria 2022)

According to Zunner and colleagues' review on myokines induced by resistance training protocols, this last-mentioned training modality can factually elevate BDNF levels; (Zunner 2022) it nevertheless must be said that the review included protocols with elderly but no studies concerning older individuals with AD were included.

Assuming that a combination of mental and physical training has greater effects on neurogenesis and neuronal survival than either training alone Sungkarat and colleagues suggest that Tai Chi, which is a discipline with special focus on mind-body exercise, may be particularly beneficial for BDNF upregulation. It is also proposable for older adults, given that it is not vigorous intensity. The researchers explain that increased BDNF levels can be influenced by the additional attention and/or social interaction experienced thanks to the intervention operating methods. (Sungkarat 2018)

Aerobic exercise programs seem to increase BDNF levels, but varying the dose and intensity of exercise may impact the results: BDNF levels are increased after a single bout of exercise, especially with high intensity training. It is also plausible that a single bout of aerobic exercise has minimal to no immediate effect on BDNF levels in neurological populations, where the increase in BDNF seen with a program of exercise could be due to a cumulative dose of regular exercise instead. We should consider the hypothesis that BDNF polymorphism is associated with its decreased activity-dependent release and so there is less of this molecule circulating. (Mackay 2017)

2.3.3 PGC-1 Alpha and Irisin

PGC1-α is a transcriptional coactivator that stimulates the expression of numerous gene products from muscle, including fibronectin type III domain-containing protein 5 (FNDC5). FNDC5 gene encodes a membrane protein that is proteolytically processed to form a new hormone secreted in the blood: Irisin. (Flori 2020)

This myokine can be produced in muscle, adipose tissue, bone and in the myocardium. Contracting muscle seems to be the main source of this myokine production in the human body. (Trettel 2023)

It is proposed to be an exercise induced molecule: exercise induces an increase in the expression and activity of muscle PGC-1α, which is accompanied by greater FNDC5 membrane expression. FNDC5 is cleaved, releasing irisin, which then enters the circulation. In the adipose tissue, Irisin is able to induce the browning of white adipose tissue, a process that increases thermogenesis and enhances energy metabolism. FNDC5 exhibits its activity via mitochondrial uncoupling protein type-1 (UCP-1), which leads to increased heat production and activation of non-shivering thermogenesis. This activity is associated with an increase in the mitochondrial-rich adipocyte population within the fat tissue and energy expenditure by these cells. (Trettel 2023)

Furthermore, Irisin improves glucose homeostasis and lipid metabolism, and reduces insulin-resistance as well as adipose tissue inflammation.

An important benefit for the myocardium is the reduction of endothelial function abnormalities. Interestingly in some findings, cardiac FNDC5 was highly expressed after exercise, and more irisin was produced in cardiac muscle than in skeletal muscle. (Chen 2022)

Additionally, Irisin seems to enhance bone mass with positive effects on cortical mineral density and bone geometry. This can be explained by irisin's inhibition of adipogenic differentiation to facilitate the osteogenic one. (Madhu 2022)

In active skeletal muscle, irisin is not only able to start mitochondrial biogenesis, but it also influences the redox status. (Trettel 2023)

Concerning neurological diseases, Irisin has positive effects on Alzheimer's disease by reducing insulin-resistance and improving glucose metabolism. Irisin is also involved in the process of neurogenesis in the CNS. (Zunner 2022) The activity of the FNDC5/irisin protein activates MAP-kinase cascades, and upon activation, the differentiation of neural cells (Nay 2021, Trettel 2023)

Through hyperphosphorylation of MAPKs and reduction of release of pro-inflammatory cytokines it exerts inhibitory effects on inflammation. It crosses the BBB and initiates neuroprotective genetic programs in the hippocampus, which leads to higher expression of BDNF and promotion of synaptogenesis and neuronal cell survival. Moreover, it reduces the release of inflammatory factors IL-6 and IL-1β, decreases Aβ protein and tau protein formation.

According to Chen and colleagues, some studies confirmed the association between irisin and risk factors of AD and showed lower irisin levels in the hippocampus and cerebrospinal fluid (CSF) of patients with AD. In contrast, the relationship between higher irisin levels in the CSF and better cognitive function, and less amyloid-β pathology is observed in both patients with AD and non-AD. (Chen 2022)

Irisin circulating levels positively correlate with skeletal muscle mass and aerobic capacity. (Nay 2021) In response to exercise, irisin regulation depends on the specific training protocol (intensity, duration, and type of exercise), age, sex, training status, and muscle mass. (Trettel 2023)

According to Zunner and colleagues review resistance exercise seems to benefit more than aerobic training modality when we refer to irisin levels, although there are still contradictory results concerning training protocols. (Zunner 2022)

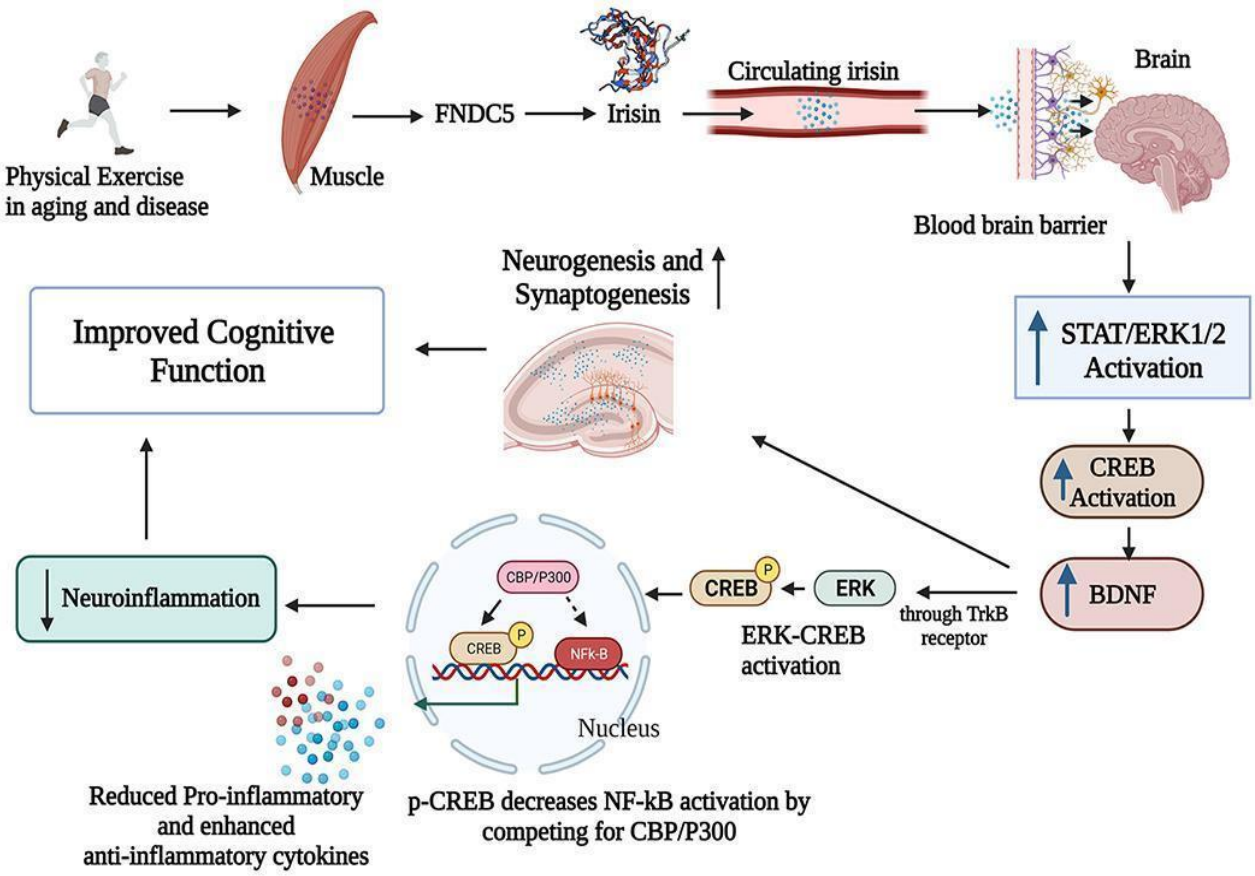

Figure 10. A schematic showing the potential mechanisms by which physical exercise-mediated irisin release could improve cognitive function in ageing and neurodegenerative disease conditions.

Physical exercise can induce FNDC5 expression in skeletal muscles. FNDC5 protein is then cleaved into irisin, which enters the circulating blood. Irisin can enter the brain by crossing the BBB, where it can increase BDNF production through the activation of STAT3/AMPK/ERK signalling, enhancing neurogenesis and synaptogenesis to improve cognitive function. Also, irisin-mediated BDNF increase has the promise to decrease neuroinflammation by reducing the production of NF-kB and pro-inflammatory cytokines IL-6 and IL-1β by activating the ERK-CREB pathway through its receptor trkB.

Figure comes from Madhu LN, Somayaji Y, Shetty AK. Review "Promise of irisin to attenuate cognitive dysfunction in aging and Alzheimer's disease." Ageing Res Rev. 2022

2.3.4 Kynurenine

Kynurenine (Kyn) is a metabolite of the amino acid L-Tryptophan and is shown to be involved in the modulation of the immune system and CNS. Alteration of Kyn pathway metabolism triggering an accumulation of the Kyn pathway metabolites is implicated in neurodegeneration. Notably, Kyn aminotransferases (KATS) are responsible for the conversion of Kyn into kynurenic acid (KynA) and are increased in habitually exercise-trained skeletal muscle. The same enzymes can be found in astrocytes, where the same transformation into KynA takes place. (Delezie 2018) Exercise increases the expression of KATs through PGC-1α in both mouse and human skeletal muscle, which results in an increase in the peripheral Kyn-to-KynA conversion and thereby restrains the accumulation of Kyn and its downstream neurotoxic metabolites in the brain. Delezie reported that observation in healthy individuals confirmed that regular endurance training promotes skeletal muscle KATs gene and protein expression, along with enhanced peripheral conversion of Kyn to KynA. (Delezie 2018)
Notably, in mice, this detoxification mechanism was shown to reduce Kyn-induced excitotoxicity, neuroinflammation, and depressive-like behaviour.

Information for this paragraph comes from Nay and colleagues review "Molecular Mechanisms Underlying the Beneficial Effects of Exercise on Brain Function and Neurological Disorders" 2021

2.3.5 FGF21

Fibroblast growth factor 21 (FGF21) is an endocrine hormone identified as an exerkine which is only in part produced by muscle. FGF21 is partly expressed by the adipose tissue and predominantly expressed by the liver during prolonged fasting, presumably via PPARα- and PGC-1α dependent mechanisms, resulting in a modulation of systemic energy balance, insulin sensitivity, hepatic gluconeogenesis and glucocorticoid levels. (Delezie 2018)
Rodent studies have shown that FGF21 stimulates the oxidation of fatty acids, ketogenesis, gluconeogenesis and inhibits lipogenesis in the liver. Acute exercise increases immediately the circulating levels of FGF21 in healthy individuals (Sabaratnam 2022). FGF21 levels increase during exercise and remain elevated for ~4 hours. The exercise-induced increase in

FGF21 seems to be liver-derived (Delezie 2018, Townsend 2021) and mediated by the glucagon to insulin ratio in humans. (Townsend 2021)
Proposed effects for FGF21 in the nervous system are the modulation of the sympathetic nerve input to brown adipose tissue, the control of circadian behaviour, and neuroprotection. (Delezie 2018)

2.3.6 Meteorin-Like

Another myokine which depends on PGC-1 Alpha is Meteorin-Like. This seems to be inducible by exercise. It can induce the browning of white adipose tissue, not by direct action on adipocytes but rather via recruitment of IL-4 and IL-13 expressing eosinophils in adipose tissue. (Zunner 2022)

2.3.7 Cytokines group: IL-6 and IL-15

Interleukin-6 (IL-6) is a proinflammatory cytokine that also has anti-inflammatory capacities when it is released by the working muscle. IL-6 circulating levels seem to transiently and rapidly increase up to 100-fold in humans after acute exercise.
Normally, levels return to baseline in 2 or 3 hours after exercise. Intriguingly, acute exercise also increases the adipose tissue transcript levels of IL-6 in healthy lean and overweight/obese individuals and remains elevated up to 2 hours into recovery. It has also been suggested that exercise-induced reductions in visceral adipose tissue mass in response to 12 weeks of exercise training is regulated by IL-6 signalling. (Sabaratnam 2022)
Instead, chronic high circulating levels of IL-6 are associated with inflammation.
IL-6 seems to cause the production of other anti-inflammatory cytokines and to inhibit the production of Tumour necrosis factor-alpha (TNF-alpha) and Interleukin-1 beta (IL-1 beta).
Another important target for IL-6 is the metabolic system where it plays an important regulatory role by enhancing insulin-sensitivity and the accumulation of glucose transporter type 4 (GLUT4). Townsend and colleagues reported that it was shown that IL-6 increases AMPK phosphorylation, stimulates GLUT4 translocation, and increases glucose uptake in neuronal cells. This is particularly relevant since insulin resistance and perturbed energy metabolism develop in brains of AD and dementia patients. (Townsend 2021)
IL-6 exerts its effect both locally and peripherally in a hormonelike fashion. It is also involved in stimulation of satellite cells' multiplication in the muscular system, leading to

protein synthesis in myotubes via activation of the mTOR- signal cascade and so, leading to hypertrophy. (Zunner 2022)

IL-15 is highly expressed in skeletal muscle. Studies conducted on murines myotubes suggest that IL-15 activates a signalling pathway which results in GLUT4 translocation increase and thereby leads to enhanced glucose uptake. Other data on mouse models collectively suggest that an increased production and release of IL-15 from skeletal muscle into the circulation may benefit systemic metabolism, possibly through its autocrine/paracrine/endocrine effects. Nevertheless, the physiological role of this molecule in humans remains unclear, together with its muscle protein content or its circulating levels. As Sabaratnam and colleagues explain, even if in most studies an exercise-induced increase in plasma IL-15 is evident, the absence of changes in muscle gene expression of IL-15 suggests that other tissues are responsible for the increase in plasma IL-15 in response to exercise. IL-15 molecular level responses to exercise require therefore future investigations. (Sabaratnam 2022)

2.3.8 Other exerkines: CTSB, Apelin

Cathepsin B (CTSB) is a protease involved in intracellular protein degradation and can also be secreted into circulation. Through its proteolytic activity, cathepsin B has been shown to reduce levels of amyloid-β plaques in a mouse model of AD. (Townsend 2021) It is also implicated in various other physiological processes, such as processing of antigens in the immune response, hormone activation and bone turnover. (Nay 2021)
Cathepsin B seems to be an exerkine induced by aerobic training. For example, 4 months of treadmill exercise training increased circulating cathepsin B in healthy humans. Interestingly, in healthy adults, there was a positive relationship between the change in circulating cathepsin B following exercise training and complex object recall tests, which is used as an indicator of hippocampal function. Conversely, CTSB knockout mice are resistant to the effects of voluntary exercise on hippocampal growth and resultant improvements in cognitive function. (Townsend 2021)
Other studies suggest that CTSB is ubiquitously expressed and upregulated in skeletal muscle after 11 weeks of strength training in healthy volunteers. (Nay 2021)

Apelin, which belongs to the APJ-axis, is widely distributed in the body and play an important role in cell protection in many organs. Apelin was discovered as an exercise-

induced myokine with an increased expression level after performing an 8-week endurance training program in 11 obese non-diabetic male subjects. These molecules are distributed throughout the nervous system and have been reported to possess neuroprotective effects, even though studies which associate Apelin and neurodegenerative diseases are insufficient. (Lee 2021)

Table 1. Exerkines

Myokine/ hepatokine	Family name	Main locations of expression	Can it pass BBB	Positive association in the nervous system	Effects	Exercise-induced effects on myokine
Myostatin	Transforming growth factor β superfamily	Muscle, adipose tissue	-	Acting on risk factors (obesity, insulin-resistance)	Limit hypertrophy ⊣Mtor →AMPK	Contradictory results (different study groups and exercise protocols)
Decorin		Muscle and adipose tissue		Acting on risk factors	Suppression of Myostatin and promotion of hypertrophy	Contradictory results (different study groups and exercise protocols)
Follistatin	Transforming growth factor β superfamily	Liver, muscle cells, adipose tissue		Acting on risk factors	Suppression of Myostatin; ↑proliferation of satellite cells Positive effects on metabolism FST can suppress the follicle-stimulating hormone (FSH)	FST plasma/serum levels are increased in response to acute exercise independent of exercise (resistance, endurance, HIIT). In elderly individuals, regular PA increases its basal concentration. (Domin)
Brain Derived Neurotrophic Factor (BDNF)	Neurotrophin family	CNS and PNS Skeletal muscle cells, cardiac myocytes, smooth muscle cells, cells in the liver	No	Improvements in memory and recollection; restraint of cognitive decline Differentiation of neurons, synaptic plasticity and neurogenesis in the amygdala, prefrontal cortex and hippocampus; at NMJ motor neuron viability, enhancement of ACh presynaptic release, and postsynaptic maintenance ↓ production of toxic amyloid β peptides	*See left.* Enhances lipid oxidation in skeletal muscles via AMP-activated kinase activation (Domin)	Exercise increases BDNF in the brain, plasma, and skeletal muscles. BDNF rises after PE in healthy adults after acute bouts of exercise and after regular exercise. (High intensity exercise and more extended training lasting at least 12 weeks show greater results) (Domin)
Irisin	PGC-1 alpha group	Skeletal muscle, adipose tissue, bone and cardiac myocytes	Yes	Positive effects on AD: ↓ of insulin-resistance and improvement of glucose metabolism. Also involved in neurogenesis in the CNS (cAMP→PKA→CREB→↑ BDNF) Inhibitory effects on CNS inflammation ↓Aβ protein and tau protein formation	Browning of white adipose tissue: ↑thermogenesis and enhances energy metabolism Improves lipid metabolism; ↓ adipose tissue inflammation Improves glucose homeostasis, ↓ insulin-resistance; enhances bone mass Positive correlation with skeletal muscle mass and aerobic capacity	↑PGC-1α, accompanied by ↑FNDC5 membrane expression; Resistance training seems to benefit more than aerobic training modality but increase Irisin levels.
Kyneurine	Metabolite of the amino acid L-Tryptophan	Predominantly in the liver		In mice, the detoxification mechanism (conversion from Kyn to KynA) was shown to reduce Kyn-induced excitotoxicity, neuroinflammation, and depressive-like behaviour		↑Kyn aminotransferases
FGF21	Endocrine FGFs	Liver, skeletal muscle cells, adipose tissue	yes	Control of circadian behaviour, and neuroprotection	Modulation of systemic energy balance, insulin sensitivity, hepatic gluconeogenesis and glucocorticoid levels. Modulation of the sympathetic nerve input to brown adipose tissue.	Acute exercise increases circulating levels in healthy individuals (up to ~4 hours).
IL-6	Cytokine group	Immune cells, muscle	yes?	↑glucose uptake via GLUT4 translocation in neuronal cells	IL-6 causes the production of other anti-inflammatory cytokines and inhibits the production of TNF-alpha and Interleukin-1 beta Promotes glycogen breakdown. Enhances insulin-sensitivity and the accumulation of GLUT4. It stimulates satellite cells' multiplication in the muscular system (mTOR signal cascade which leads to hypertrophy) In adipocytes it induces lipolysis and free fatty acid oxidation	IL-6 circulating levels increase up to 100-fold in humans after acute exercise (up to ~2-3 hours)
IL-15	Cytokine group	Immune cells, muscle	yes?	↑ glucose uptake via GLUT4 translocation in neuronal cells.	Immune cell proliferation, differentiation and maturation. Immune response regulation. Muscle protein synthesis. Adipose tissue reduction. Glucose metabolism regulation.	Relationship between IL-15 and muscle needs future research
Cathepsin B	Protease	Skeletal muscle cells	Yes	↓ levels of Aβ plaques in a mouse model of AD.	*See left.*	4 months of treadmill exercise led to a significant increase of plasma CTSB concentrations in rhesus monkeys and humans. (Delezie)
Apelin	APJ-axis	Liver, CNS, cardiovascular system	Yes?	Neuroprotective effects	Cell protection in many organs	Expression level increased after performing an 8-week endurance training program in 11 obese non-diabetic male subjects

Table legend: Aβ=Amyloid beta; Ach=Acetylcholine; AD=Alzheimer's Disease; AMPK=AMP-activated protein Kinase; APJ=Apelin protein-coupled receptor; BBB=Blood Brain Barrier; cAMP=cyclic adenosine monophosphate; CNS=Central Nervous System; CREB=cAMP response element-binding protein; CTSB=Cathepsin B; FGF=Fibroblast growth factor FNDC5=fibronectin type III domain-containing protein 5; FST=Follistatin; GLUT4=glucose transporter type 4; HIIT=High Intensity Interval Training; IL-6=Interleukin-6; IL-15= Interleukin-15; Kyn= Kynurenine; Kyn A= kynurenic acid; mTOR: mammalian Target of Rapamycin; NMJ=Neuromuscular Joint; PA=Physical Activity; PGC-1alpha=Peroxisome proliferator-activated receptor-gamma coactivator; PKA=Protein Kinase A; PNS=Peripheral Nervous System; TNF-alpha=Tumour necrosis factor-alpha

3 EXERCISE

As we discussed the general health benefits of physical activity, we understood how extensive the room of improvement can be, in any given population. It can act as a free preventive tool which ancestrally belongs to us humans and has many pathways through which it can operate.
Based on that, it is of utmost importance to find a common training program, or at least common programs design features which take into account all possible PA effective mechanisms to prevent or at least reduce the development and worsening of cognitive decline.
Studies have proposed that Aerobic exercise is likely to exert its effects via mechanisms distinct from those of Resistance exercise. (Azevedo 2023) We saw that myokines have their role in this, therefore let's simply analyse some exercise protocols which take them into consideration, focusing on studies conducted in elderly individuals and people with MCI or previous AD stages.

3.1 Exercise and cognitive function

Demurtas and colleagues in their review under the title "Physical Activity and Exercise in Mild Cognitive Impairment and Dementia: An Umbrella Review of Intervention and Observational Studies" considered the following types of exercise and PA: aerobic exercise, resistance exercise, balance and coordination exercise, motor-cognitive interventions (Virtual Reality, Exergaming), mixed programs, physiotherapy, and physical activity during occupational therapy. Their findings suggest that PA/exercise significantly improved global cognition. In people with MCI were found beneficial effects on attention, executive functions and memory while in people with dementia general ameliorated cognitive function was found, without any specific domain distinction. (Demurtas 2020)
Erickson and colleagues examined whether physical activity interventions enhance cognitive and brain outcomes across the lifespan even in populations experiencing cognitive dysfunction. Their findings confirmed with strong evidence that greater amounts of PA are associated with a reduced risk of developing cognitive impairment, including Alzheimer's disease. In adults with dementia, moderate evidence suggests that PA may improve cognitive function; moreover, the researchers claim that adults with risk of dementia or with cognitive

disorders which perform greater amounts of PA would reduce the risk for cognitive impairment, the average decrease of which seems to reach 40% in most prospective studies. (Erickson 2019)

What about memory?

While observing and studying memory after an exercise bout, scientists and researchers could find wide discrepancy, which is possibly related to the fatigue which interferes with the cognitive responses. Moreover, results may differ based on the memory tests, the temporality of memory assessment, the time elapsed from completion of the exercise, and the method of estimating the intensity of exercise training. Nevertheless, it seems that regular chronic type of training is more prominent for memory facilitation.

Interestingly, it seems that beneficial effects of exercise on brain structures are mostly found in the regions sensitive to neurodegeneration such as the hippocampus and the neocortex in healthy elderly and in adults with Alzheimer's disease or Mild Cognitive Impairment as well. As we have seen before, regular PA improves brain circulation in aged subjects. This higher cardiorespiratory fitness has been found to be associated with greater brain structure integrity, how for white matter increase in people with MCI, and better memory performance.

After 6 to 12 weeks of exercise training, people in the early stage of Alzheimer's disease could reduce hippocampal atrophy together with improved memory outcomes.

Babaei and colleagues' findings suggest an exercise-induced increase of noradrenaline which has a potentiating role on learning and memory as well. (Babaei 2022)

Titus and colleagues worked on a systematic review including adults over 60 years old which followed longitudinal exercise protocols (aerobic, resistance or multimodal training). They assessed that the majority of studies found positive effects on cognitive domains, for instance complex attention, executive function, learning and memory, language, perceptual motor function and global cognition. (Titus 2021)

3.2 Aerobic exercise

Aerobic exercise (we can refer to this also as cardio or cardiorespiratory exercise) refers to the type of repetitive, structured physical activity that requires the body's metabolic system to use oxygen to produce energy. It is characterised by moderate energy expenditure over a prolonged period of time. Aspecific response to endurance training is transport systems improvement, which comprehends the heart and circulatory system. (Weineck 2009)

A recent review from Ayari and colleagues aimed at measuring proinflammatory and anti-inflammatory cytokines as a result of chronic exercise protocols in both animals and humans. Their results show that cytokine levels after exercise depend on type of exercise, on both intensity and volume, on the duration of the experimental protocol and frequency of training. Regardless of these, they show that exercise generally decreases pro-inflammatory cytokines in animal models and increases anti-inflammatory cytokines in human models. Aerobic exercise inhibits the circulation of peripheral proinflammatory cytokines and only high-volume multimodal exercise has the same effect. Researchers claim that moderate-intensity or moderate-to-high intensity aerobic exercise is the most appropriate training for AD patients, whereas moderate- to high-intensity multimodal training (3 times/week) is the most effective in reducing proinflammatory cytokines and improving cognition in older people with MCI. They therefore suggest that exercising 3 times/week is effective for older people with amnestic MCI, whereas a voluntary exercise frequency is effective for older people with AD. In older people with AD, both voluntary cycling training and moderate- to- high intensity aerobic exercise are effective. It seems that exercise inhibits proinflammatory cytokines secretion and stimulates anti-inflammatory cytokines secretion regardless of gender and age. Reducing the levels of IL -1β, TNF-α, and IL -6 could be partly responsible for the beneficial effects of physical activity on cognitive performance in people with MCI and AD. (Ayari 2023)

Baker and colleagues mentioned that for humans, increased aerobic fitness in cognitively healthy older adults is associated with reduced age-related atrophy and increased perfusion in regions that support executive control and memory processes. In their controlled trial, adults with amnestic MCI (mean age, 70 years old) that followed a 6 months-long aerobic training program, with increased intensity overtime, improved in executive control processes of multitasking, cognitive flexibility, information processing efficiency and selective attention, compared to a control group who only performed stretching activities. It seems that aerobic exercise had more effects on women compared to men in some tests even though there were comparable gains in cardiorespiratory fitness. Cholesterol levels are associated with higher risk of incurring AD and this protocol succeeded in lowering those levels relative to controls. For these reasons, aerobic exercise could play a protective role by attenuating progression of cognitive symptoms in MCI. (Baker 2010)

Brinke and colleagues found that aerobic training exercise performed twice a week for six months by older women (70-80 years old) with probable MCI, increased left, right and total hippocampal volume, which is significant when we consider that hippocampal atrophy is a hallmark of AD. (Brinke 2014)

The review from Bourbeau and colleagues suggests some mechanisms through which aerobic exercise can attenuate obesity-induced cognitive impairment. A relationship between obesity (body mass index (BMI) ≥ 30 kg/m2) and deficits in cognitive function is already evident, independently of age, sex, or comorbidities of obesity. Aerobic exercise interventions may increase resting CBF to the frontal lobe and improve executive function, independent of weight loss. Individuals with obesity commonly have endothelial dysfunction, which may explain impaired CBF regulation, while aerobic exercise can bring aid to that, leading to enhanced cerebrovascular reactivity and improving vascular insulin sensitivity. The obesity status displays greater levels of neuroinflammation. Again, aerobic exercise can inhibit microglial activation through an increase in anti-inflammatory molecules (i.e. IL-6 which in turns stimulates IL-10 production) and a decrease in pro-inflammatory molecules (i.e. TNF-α and IL-1β). Furthermore, aerobic exercise can increase circulating levels of adiponectin (anti-inflammatory) and reduce circulating levels of leptin and free fatty acids (pro-inflammatory). (Bourbeau 2023)

Taniguchi et al. reported a significant decrease in serum FGF21 in older men after five weeks of regular cycling. The authors hypothesises that prolonged exercise reduced the so-called FGF21 resistance, similarly to insulin resistance, and consequently decreased FGF21 serum concentration. (Domin 2021)

Interestingly aerobic exercise seems to promote Aβ efflux by upregulating LRP1 and downregulating RAGE, which contributes to Aβ transport in the brain for peripheral clearance. (*see chapter 1.3.6)* (Xu 2023)

3.3 Neuroprotective effects of resistance PE on the APP/PS1 mouse model of AD

In animal models, RE was able to promote the clearance of Aβ, reduce the volume and number of Aβ plaques, and reduce tau pathology in the brain. (Azevedo)

In experimental models using transgenic mice to study AD, the animals present Aβ accumulation and plaque formation in the prefrontal cortex and hippocampus, as well as elevated plasma corticosterone levels and hyperlocomotion in the open field test. According to some studies, high levels of corticosteroids in the brain of AD animals lead to increased activation of BACE1 that, in turn, processes (cleaves) APP forming the Aβ neurotoxic peptide. On the contrary, animals exposed to physical exercise have lower levels of corticosterone, along with cognitive improvements and reduction of Aβ load in the hippocampal region.
What if they undergo a designed Resistance exercise program? The article from Campos and colleagues "Neuroprotective effects of resistance physical exercise on the APP/PS1 mouse model of Alzheimer's disease" tried to answer this specific question.

How is the experiment carried out?
Selected animals are 6–7-month-old APPswe/PS1dE9 transgenic mice divided into two groups, one of which followed a Resistance exercise training every other day for four weeks, and a control group negative for the mutation; RE protocol consisted in climbing a ladder with progressive overload. At the end of the program mice are tested in an open field, locomotor activities and anxiety-related behaviour being evaluated. Twenty-four hours later, the novel object recognition test was performed as well. Plasma corticosterone was analysed through blood samples and brains were removed from the skull, frozen, coronally sectioned immunostained with the Aβ and the microglia protein marker.

According to Campos and colleagues' results, RE reduced the number of Aβ plaques in the hippocampus of these animals.
Interestingly, RE increased the number of microglial cells in the hippocampus of APP/PS1 mice. These cells seem to be preferentially located around the plaques, and the number and area covered by microglia marker positive cells surrounding the β-amyloid plaques were increased in APP/PS1+RE mice, but not in the transgenic sedentary animals. In fact, it has been described that exercise is capable of reducing neuroinflammation by modulating microglial activation, and consequently diminishing pro-inflammatory cytokine levels and improving the pathogenesis of AD.
Since increased levels of corticosterone induces activation of BACE1 scientists speculate that the decrease in corticosterone levels induced by RE contributes to the decrease in

hippocampal Aβ plaques of APP/PS1 mice. Together, these factors may have contributed to the normalisation of locomotor behaviour in APP/PS1 animals subjected to RE.
To summarise, when applied to transgenic mice, daily RE promotes the control of hyperlocomotion, reduction of Aβ load in the hippocampus and decreased pro-inflammatory cytokine levels.
Therefore, resistance exercise can improve brain function in the elderly and can be neuroprotective, reducing the risk for the onset of AD and other dementia. Evidence suggests that when exercise is introduced into the pre-plaque phase there is less Aβ deposition, so exercise would be more effective in improving AD in the early stages.

Information for this paragraph comes from Campos and colleagues' article "Neuroprotective effects of resistance physical exercise on the APP/PS1 mouse model of Alzheimer's disease" 2023

3.4 Resistance exercise

Resistance Exercise (RE) is the common term used to describe activity of voluntary contractions of specific muscles against external resistance. Among the general outcomes of practising resistance training, we can find improved muscle mass and strength, bone density, overall body composition, as well as functional capacity and balance. This kind of benefits counts even more if we consider older people's needs linked to frailty and higher risk of musculoskeletal diseases. The main question remains whether positive effects of this type of exercise on myokines are also valid for the elderly, that is the population of our interest, and whether they're related to brain health.

Regarding Resistance training Matta Mello Portugal and colleagues review "Aging Process, Cognitive Decline and Alzheimer's Disease: Can Strength Training Modulate These Responses?" reported data from different studies which show positive effects of strength training on elderly individuals:

Parise and colleagues reported the effect of strength training on oxidative stress in the elderly. They analysed the effects of strength training in subjects with a mean age of 68.5 years, after 14 weeks. The exercise protocol was preceded by a five-minute warm up in cycle ergometer and at the end of the cool-down, stretching exercises were performed. The strength training

session had twelve exercises followed by a circuit set with two minutes of rest between sets, 1-3 sets and 10-12 repetitions. The initial intensity was set at 50% of one repetition maximum (1RM) and after a set at 80% 1RM. There was a reduction in oxidative stress and an increased complex IV electron transport chain activity, which is an indirect indicator of antioxidant activity. Although these findings were based on skeletal muscle analyses, it is possible to infer a good association between mitochondrial activity on muscle and brain as well. (Matta Mello Portugal 2015)

Cassilhas and colleagues evaluated the effect of 24 weeks of strength training on neuropsychological tests and serum concentration of IGF-1 in elderly subjects between 65 and 75 years old. Participants trained four one hour, three times per week. The protocol consisted in 10-minute warm up on a cycle ergometer and stretching exercises, followed by strength training protocol with six exercises performed in two sets of eight repetitions. The intensity was set at 50% 1RM in one experimental group and in the other at 80% 1RM. There was also a control group practising the same protocol, but without any load. Both experimental groups showed increased serum IGF-1, when compared to the control group. This result suggests a positive influence of strength training on serum IGF-1 concentration and cognitive performance. Furthermore, the exercise intensity did not influence the IGF-1 serum concentration. (Cassilhas 2007)

Coelho and colleagues evaluated serum BDNF concentration and performance on the TUG (physical test known as Timed Up-and-Go, in which one must stand up from a seated position on a chair, walk three metres at a comfortable pace, turn around, walk back to the chair and sit down.) before and after a protocol of strength training for the lower limbs in non-frail and pre-frail elderly subjects. Training was performed for 10 weeks, three times a week for 60 min, with three sets of eight repetitions at 75% 1RM. At baseline, the plasma concentration of BDNF was higher in non-frail than pre-frail individuals. After training, both groups increased their concentration of BDNF. In addition, there was a significant increase in TUG performance. (Matta Mello Portugal 2015)

Analysing the strength training effects on executive function during a 52-week period in elderly women between 65 and 75 years, Liu-Ambrose and colleagues compared three groups. Two groups did strength training, one group once a week and the other one twice a week; the third group was the control. Both strength training groups improved their cognitive function and gait speed. (Matta Mello Portugal 2015)

In this context of motor improvements related to strength exercises, Hauer and colleagues analysed elderly with dementia aged 65 years or more. Two groups submitting to exercise intervention during 12 weeks were analysed.

- In one group, the subjects practised strength training at 70-80% 1RM twice a week and some exercises related to daily living activities such as sitting down and standing up.
- In the other group, exercises such as stretching and callisthenics were performed. The authors only reported that the intensity of these exercises was low.

The strength training group increased strength, power and motor performance in a series of tasks, when compared to baseline measurements in the other experimental group. (Matta Mello Portugal 2015)

Resistance exercise has a potential metabolic effect on insulin resistance, diabetes type 2 (DMT2) and ageing. Shabkhiz and colleagues designed a training protocol of 12 weeks with resistance exercise performed three days a week, each exercise was performed 10 times with 70% of 1RM. RE was able to decrease myostatin concentration levels and increase in muscle strength and decreased the insulin resistance index (HOMA-IR) in elderly men without diabetes. Moreover, in elderly with diabetes type 2 condition circulating myostatin levels were reduced and muscle strength increased. (Shabkhiz 2021)
On the other hand, follistatin basal concentration, which we saw having positive effects on metabolism and activation of satellite cells, are increased by regular physical activity (lasting from 2 weeks to 6 months) regardless of the training duration and the type of activity performed in middle aged and elderly. (Domin 2021)

Castaño and colleagues investigated the effects of the combination of Resistance Training and Cognitive training (verbal fluency). Participants of the study were sedentary, 60 years old or more, with sufficient physical and cognitive abilities to perform the interventions. The protocol lasted 16 weeks, with training performed twice a week, composed of progressive 2 to 3 sets of eight resistance exercises for major muscle groups (leg press, dumbbell lateral raise, lateral pulldown, abdominal crunch, back extension, seated leg curl, bench press, and standing calf raise), 8–15 repetitions at 60%–70% of 1-repetition maximum (1RM). Cognitive performance consisted in saying aloud as many words as possible of a specific

category in each exercise set. Task difficulty was increased monthly by changing the categories of words, from general to specific, whereas semantic categories (e.g., animals and colours) and phonological categories (e.g., words beginning with a certain letter) were changed in each exercise set. Even though this study did not establish cause-effect relationships, results indicated that resistance training in the presence or absence of cognitive training improved physical function in healthy older adults but only the group which performed the combination of the two improved cognition, semantic and phonological verbal fluency, and plasma BDNF levels. They suggest that interventions of at least 6 months seem to be necessary to elicit significant changes in cognitive parameters. In this study there is a near-transfer effect in cognitive training, because of the learning stimulus being similar to that of the tests. Therefore, their study corroborates the difficulty in generating far transfer for other cognitive adaptations that are not similar to task and/or type of stimulus. (Castaño 2022)

Some attention should be paid to the duration, or rather the continuance of exercise protocols too. One study from Nuvagah Forti and colleagues, followed older male participants through 12 weeks exercise intervention, dividing them into groups to assess the preferential intensity training modality in order to increase BDNF circulating levels. At the end of this intervention period, results suggest mixed-low resistance training to be more effective for their purpose. Researchers then analysed the effect of 24 weeks of detraining in the same population, ending up discovering that BDNF levels reduced back to baseline levels. This surely suggests that continuous exercise adherence seems necessary to sustain the training-induced effects on BDNF in older persons. (Nuvagah Forti 2017)

The studies from Tsai and colleagues and their results are intriguing: they recruited elderly male participants and randomised them to a control or exercise group. 1-RM and peak muscle power were assessed, baseline blood samples withdrawn and cognitive task test (Oddball test) with concomitant neuroelectric recording was performed. After 12 months, the participants completed the same questionnaires, had blood withdrawn, and received measures of neurocognitive parameters. The exercise protocol was a circuit training schedule with a progressive, high-intensity protocol, with three sets of ten repetitions at 75–80% 1- RM, at an average speed, with a 90-second rest between sets, and a 3 min interval between each apparatus. This was performed three times a week for 12 months.

At the end of the program, the control group displayed a lower accuracy rate when performing the oddball test, whereas long-term resistance exercise seems to be an effective mechanism for attenuating the age-related decreases in neural efficiency in healthy elderly individuals manifested during the oddball task, possibly modulated by increased IGF-1 levels. Furthermore, the increased IGF-1 levels achieved via such an exercise protocol could have positive effects on both neuropsychological and neuroelectric performance in the elderly. For this reason, this study's findings imply that healthy elderly individuals who regularly engage in resistance exercise might delay the onset of age-related decline in executive functions, and that this protective effect may be modulated by the growth factor-IGF-1. (Tsai, 2015)

Another work from Tsai CL investigated the effect of an acute bout of strength exercise in older people with amnestic MCI, which led to increased serum IGF-1 levels, which nevertheless returned almost to baseline after about 20 minutes. These findings of changes in neuroprotective growth factors and neurocognitive performances through an acute bout of exercise suggest that molecular and neural prerequisites for exercise-dependent plasticity are preserved in elderly aMCI individuals. (Tsai, 2017)

This opened the doors for Tsai CL and colleagues to investigate both effects of Aerobic and Resistance training protocol on neuroprotective growth factors, inflammatory cytokines and neurocognitive performance. They recruited 55 older adults with amnestic MCI and assessed circulating BDNF, IGF-1, VEGF AND FGF-2 levels, as well as TNF-α, IL-1β, IL-6, IL-8, and IL-15 levels at baseline and after 16 weeks or exercise protocol.

Concerning the Resistance training intervention, it included both machines and free weights, with exercise protocol that included all major muscle groups. Although some parameters didn't change, they found significantly increased IGF-1 levels and decreased IL-15 levels, together with some facilitation in neurocognitive performance. (Tsai, 2019)

Azevedo and colleagues in their review named "The effects of resistance exercise on cognitive function, amyloidogenesis, and neuroinflammation in Alzheimer's disease" reported that RE is effective in treating cognitive function and memory in patients with MCI or AD. Training frequency, intensity and duration are important factors to consider when designing the training schedule. Human studies investigating the effects of RE in the elderly population have indicated that 12 weeks to 6 months lasting programs increase peripheral BDNF levels. RE can elevate the levels of IGF-1 and BDNF by enhancing muscle strength, increasing neurogenesis, and ameliorating insulin sensitization. Regular physical exercise

stimulates synthesis and increases IGF-1 levels, mediates hippocampal neurogenesis, and induces neuroprotection. (Azevedo 2023)

Patients with MCI, which present low IGF-1 levels in the brain, when practising RE can elevate those levels, therefore helping to increase synaptic plasticity, neuronal survival, and cognitive performance, improving AD pathophysiology. (Azevedo 2023) Progressive resistance training performed 2-3 times a week for six months in older adults with MCI was effective in improving cognitive function. Similar interventions should be optimised to maximise strength gains which can lead to cognition improvements, for example preferring high intensity resistance training to low-to moderate intensity, which was shown to have less effects in strength gains in these populations. (Mavros 2017)

Chupel and colleagues investigated how chair-based elastic bands resistance training protocol could influence blood haematological markers and inflammatory balance in older women with cognitive impairment. After 28 weeks of training, during which the resistance offered by elastic bands was increased, functional fitness and anti-inflammatory cytokine concentrations together with the attenuation of inflammation and improvement of global cognition were found. Compared to the control group, which didn't perform any type of training, older women that underwent strength training were able to improve their performance on the MMSE tasks and to increase their global cognition. These results suggest that physical activity could help attenuate cognitive decline over time, this being partly explained by the increases in IL-10 and maintenance of TNF-α levels, switching to better inflammatory balance ratios. It is interesting to notice, that in the control group TNF-α/IL-10 ratio didn't change, but there was an increase in C-reactive protein (CRP), together with a slight decrease in cognition.
The study intervention led to a decrease in granulocyte counts which was associated with the increase in cognition. Instead, there is a relationship between high blood cell counts and low cognition, supporting the idea that vascular inflammation induced by ageing can affect cognition. (Chupel 2017) Beneficial anti-inflammatory effects of strength training are confirmed in older females' patients with MCI. (Ayari 2023)

Concerning the myokine irisin, the studies from Kim (Kim 2015) and Zhao (Zhao 2017) on respectively female and male older adults showed very high and significant increase of

circulating irisin, based on what is reported in the review from Cosio and colleagues “Effect of Chronic Resistance Training on Circulating Irisin: Systematic Review and Meta-Analysis of Randomized Controlled Trials”. According to their results, higher intensity (60 to 85% 1RM) and progressive resistance training programs result in significant increases in circulating irisin. Surprisingly they also found that shorter periods of training seem to be more effective in increasing circulating irisin levels, but this could be linked to this molecule’s short life expectancy hypothesis. (Cosio 2021)

Table 2. Summary of RE protocols

First author	Subjects age	Protocol duration	Was there a progression?	Frequency/week & sets per repetition		Training load	Outcomes	Observation
Parise et all.	Elderly, mean age 68.5 years old	14 weeks~ 3.5 months	-		1-3 sets x12 reps of 12 ex. + circuit set (2 min. rest btw sets)	50% 1RM the 1st set, then 80% 1 RM	↓Oxidative stress and ↑ Complex IV electron transport chain activity	Whole body exercises were selected.
Cassilhas et all.	Elderly, aged btw 65 and 75	24 weeks~ 6 months	-	3/w	2x8 reps of 6 ex.	50% 1RM or 80% 1RM	↑IGF-1 serum concentration and cognitive performance	No preference for one intensity zone.
Coelho et all.	Non-frail and pre-frail older adults	10 weeks~ 2.5 months	-	3/w	3x8 reps	75% 1RM	↑BDNF levels in both groups. ↑TUG performance	Exercises for lower limbs were performed.
Liu-Ambrose et all.	Older women aged btw 65 and 75	52 weeks~1 year	-	1/w or 2/w			↑Cognitive function ↑Gait speed in both groups	
Hauer et all.	Elderly with dementia, aged ≥65	12 weeks~ 3 months	-	2/w		70-80% 1RM	↑Strength, power and motor performance	Exercises similar to daily activities were performed.
Shabkhiz et all.	Elderly men without and with DMT2	12 weeks~ 3 months	-	3/w	10 reps for ex.	70% 1RM	↓Myostatin concentration levels, ↑Muscle strength, ↓ HOMA-IR in elderly without DMT2; ↓Myostatin concentration levels, ↑Muscle strength in elderly with DMT2	
Domin et all.	Middle aged and elderly individuals	2 weeks~ 6 months	-	Regular			↑Follistatin basal levels	
Castaño et all.	Sedentary individuals, aged ≥60	16 weeks~4 months	Yes	2/w	2-3x 8-15 reps of 8 ex. with 1'30" rest btw sets and 3' rest btw apparatus	60%-70% 1RM	↑Physical function for all groups. ↑Cognition, semantic and phonological verbal fluency. ↑Plasma BDNF levels in the group that performed RE+ cognitive training	Exercises for major muscle groups were performed.
Nuvagah Forti et all.	Older male participants	12 weeks ~3 months	-			Different intensity modalities	Mixed-low intensity RE seems to be more efficient to ↑BDNF circulating levels	
Tsai et all. (2015)	Elderly male participants	12 weeks~ 3 months	Yes	3/w	Circuit training: 3x10 reps.	High intensity: 75–80% 1- RM	↑IGF-1 levels	IGF1 is thought to be responsible for attenuating the age-related decreases in neural efficiency during the oddball task and is beneficial for neuropsychological and neuroelectric performance.
Tsai CL. et all. (2019)	Older adults with amnestic MCI, mean age 65.4 ± 6.8	16 weeks~ 4 months	Yes	3/w	3x10 reps with 90'' btw sets and 2' btw ex.	60 to 70% of 1RM in the first 2 weeks and at 75% of 1RM in the remaining weeks	↑Serum IGF-1 levels ↑Cognitive performance ↓Serum TNF-α levels ↓Serum IL-15 levels	Exercises for major muscle groups were performed (e.g., biceps curls, vertical butterflies, leg press, seated rowing, hamstring curls, and calf raises).
Mavros et all.	Older adults with MCI	6 months	Yes	2/w or 3/w			Improved cognitive function	High intensity> low intensity for strength gains.
Chupel et all.	Female participants, mean age 82.7 ± 5.7 years with moderate or mild cognitive impairment	28 weeks~ 7 months	Yes, by changing the elastic-band colour from yellow (less resistance) to red (greater resistance)	2/w or 3/w	8-10 elastic-band exercises using the yellow and red colours levels of elastic bands	Values of Perceived exertion scale between 6 and 8 levels (somewhat hard and hard).	↑Anti-inflammatory cytokine concentrations total ↑global cognition ↑Physical performance. ↓leukocyte and lymphocyte numbers	Chair based strength training with elastic bands.
Kim et all.	Female older adults, mean age 75 years	12 weeks	Yes, both in volume and training intensity	3/w	2–3 x 12–15 reps	Borg RPE 12–13	↑Circulating irisin levels ↑Isokinetic leg strength and grip strength	Elastic band training; they also performed stretching exercises once a week for one hour.
Zhao et all.	Male older adults mean age 62	12 weeks	Yes	2/w	6 machine-based ex 2–4 x 5–12 reps + 5 CORE ex.	70-85% 1 RM	↑Circulating irisin levels	

Table legend: 1-RM=One Repetition Maximum; w=week; BDNF=Brain Derived Neurotrophic Factor; Btw=between; DMT2: Diabetes Mellitus Type 2; Ex=exercises; HOMA-IR=Homeostatic Model Assessment for Insulin Resistance; IGF-1=Insulin Growth Factor 1; IL-15=Interleukin-15; MCI=Mild Cognitive Impairment; RE= Resistance Exercise; Reps=repetitions; RPE=Ratings of Perceived Exertion; TNF-α=Tumor Necrosis Factor-α; TUG=Timed Up and Go (test).

3.5 Is there a perfect training program to prevent or delay the onset of Alzheimer?

As we discussed different training modalities and their outcomes, it is clear how different results can be reached through various ways. And, even when protocols seem similar, outcomes can be the most variable. Duration, intensity and frequency of exercise are only examples of training variables. In many studies, researchers and kinesiologists give some references and suggestions for future research modality, showing that the sport science and fitness sector are evolving, trying to become increasingly specific in relation to the population's physical and psychological needs. What we've been focusing on is cognitive function improvement and the prevention of its declinement through exercise. In this case, training should rather be tailored to older adults, whose responses to training and physiological needs are undoubtedly different from those of the young population.
Greater amounts of physical activity are associated with a reduced risk of cognitive decline and dementia, including AD. (Erickson 2019, Northey 2018) It's important to affirm that interventions which are carried on in the previous stage of cognitive impairment are more likely to bring greater benefits.
Xu Liya and colleagues emphasise that we must follow scientific and safe principles, adopt reasonable exercise methods, make older adults engage regular scientific exercise, improve the body ability and cardiopulmonary function, and provide conditions for the older adults to maintain continuous training. (Xu Liya 2023)
For example, acute unaccustomed or exhaustive exercise might result in an increased production of ROS, while regular exercise training has been proven to decrease biomarkers of inflammation (e.g., IL-6, C-reactive protein) in the elderly and in individuals with cognitive impairments, thereby promoting brain health. (Valenzuela 2020)
Moreover, I would suggest, when possible, to implement some progression to the training program, after a first period spent learning movements and exercise, so there could be major adaptations over time, especially in resistance training.

Considering training protocols benefits dictated by myokines secretion, the main articles and reviews on the topic suggest at least 6 months of training in order to see proper results. (Castaño 2022, Chupel 2017) Moreover it should be pursued with constancy. (Nuvagah Forti 2017)
Exercise improves cognitive function in older adults in an intensity-dependent manner. (Lu 2023) Larger effects were observed with PA bouts of moderate to vigorous intensity,

(Northey 2018) lasting 46–60 min (compared with exercise bouts lasting 15–30 and 31–45 min) (Erickson 2019, Northey 2018) in interventions lasting for at least 6 months. (Erickson 2019) Again, it is suggested to keep a high frequency of training during the week. (Northey 2018)
The group of Valenzuela reported that 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 seem to be dependent on lactate production. Intense exercise sessions (i.e., relying mainly on aerobic/anaerobic glycolysis, and thus resulting in higher lactate levels) might be a suitable type of exercise against AD risk, not only in middle-aged adults but also in older people. (Valenzuela 2020)
Moderate-intensity exercise has been suggested as an optimal intensity for promotion of mental health by decreasing the level of TNF-α.

Then, what training modality should be preferred?
When both types of exercise were compared, studies have suggested that resistance exercise elevates IGF-1 levels more than BDNF in the hippocampus and peripheral blood, whereas aerobic exercise preferentially increase BDNF more than IGF-1, (Azevedo 2023)
In Northey and colleagues systematic review it is claimed that there's no certainty of resistance training being better than other modes of exercise, but it surely has particularly pronounced effects on executive function, memory and working memory. (Northey 2018)
In the section named "recommendations for future studies" of Herold and colleagues' review article, they suggest that resistance training should be designed to induce muscle hypertrophy, which pathway is linked to IGF-1. They also give some information about exercise training variables: an acute bout of moderate-load resistance exercises (70 to 100% of the 10RM, 10RM = the load needed for 10 repetitions until maximum exhaustion) improves the speed of processing, while resistance exercises with low load (40% of the 10RM) improve executive function; moderate-load (70% of 10RM) resistance exercises seem more effective in improving executive functions than low-load (40% of 10RM). (Herold 2019) Therefore, we can suggest adopting moderate intensity of training rather than lower.

Resistance training must be recommended to older adults, since it helps both preventing and fighting sarcopenia and loss of muscle strength, which are related to cognitive decline and increased AD risk. (Valenzuela 2020)

Concerning which muscles groups should have a priority and should be present in a program, we have to consider that the decline in maximum muscular strength is more serious in the lower limbs than in upper limbs, (Herold 2019) therefore I would surely suggest including exercise for the legs in the training protocol, also because of the great percentage of muscle mass they cover and their functionality in daily living activities.
It was also hypothesised that resistance exercises with blood flow restriction (BFR) could be beneficial for neurocognition because resistance exercises with BFR induce beneficial processes on a molecular and cellular level, but future research is needed. (Herold 2019) This training modality surely could be taken into consideration, given that most older adults may not be able to perform 70% of 1RM or higher intensity.

Regarding cardiorespiratory fitness and VO2max, which is correlated with the improvements in white matter tract integrity of the prefrontal cortex in individuals with MCI, HIIT might be a more efficient strategy. 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. (Valenzuela 2020)

RE combined with AE (ie, multicomponent training) yields good results in improving memory and cognitive functions and minimising AD pathophysiology. Therefore, it is plausible that the combination of different exercise modalities is more efficient in increasing cognitive reserve, (which describes the brain's functional ability to adapt and compensate for damage), and neurogenesis than exercise programs with a single type of exercise. (Azevedo 2023)
Lu and colleagues reported multicomponent training as the most effective to improve cognition among patients with MCI. (Lu 2023)
The meta-analysis from Northey and colleagues provides positive evidence for the prescription of both aerobic and resistance training, in accordance with exercise recommendations, to improve cognitive functions in people aged over 50. (Northey 2018)
Venegas-Sanabria supports the effectiveness of multicomponent physical exercise on global cognition, when the exercise protocol includes aerobic exercise, in people with MCI or dementia. The author reports that BDNF blood levels are not affected by multicomponent physical exercise interventions, the reason would be the interference between aerobic and resistance training signalling, in animal models. (Venegas-Sanabria 2022)

Some attention should be paid to sex and gender as well. As Barha points out, underlying biological differences between females and males are associated with differences in age-related physiological changes, disease risk and health outcomes. Moreover, sex influences physiological responses to exercise as well. Thus, specific forms of exercise at the same intensity and dose may have different impacts on males versus females. For females in their midlife the menopause transition (MT) negatively impacts multiple systems in the body. Notably, the MT, through loss of estradiol, significantly impacts the female brain and it predisposes women to sarcopenia and osteoporosis. (Barha 2020)
These could be some reasons why Erickson and colleagues found a greater percentage of women in studies with larger effect sizes for executive functions in adults over the age of 50. (Erickson 2019)
Speaking about gender, it seems that women benefit more than men from social interactions. (Barha 2020)

Summary

- Population of interest: Older adults
- Purpose: prevent or delay the onset of Alzheimer
- Methods: improve cognitive function, body ability and cardiopulmonary function, prevent or reduce Sarcopenia, rise myokines levels, reduce ROS production.
- Exercise features:

- Continuous (>6 months training)
- Safe
- Moderate to vigorous intensity (higher BDNF, decrease of TNF-α levels, improved executive function), occasionally including HIIT;
- RE to improve executive function, memory and working memory and higher IGF-1 levels; prevents and fights sarcopenia and loss of muscle strength;
- AE for higher BDNF levels; improves cardiorespiratory fitness and VO2max;
- Multicomponent training for memory and cognitive functions improvement and for minimising AD pathophysiology. May improve cognitive reserve and neurogenesis. Improves cognition in individuals with MCI.

CONCLUSIONS

Prevention of neurodegeneration and mitigation of its impact in life, albeit unpredictable, has a spectrum of interventions, with exercise paving an attractive way. Myokines, which are secreted with physical activity, could help monitoring exercise effects on cognition and brain health.

From reading about resistance training protocols, evidently great discrepancy between exercise training modalities makes it difficult to define with certainty how many series or which exercises could raise BDNF and other myokines levels at the utmost. However, we could observe greater global cognition and physical performance following these types of training interventions.

All that should encourage researchers and kinesiologists to include and support resistance exercise into training for older adults with prodromal signs of cognitive decline, e.g., people with diagnosed MCI. Implementing these disease-modifying therapies in preclinical phase of AD is the most appropriate window to alter the disease course.

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FIGURES

Figure 1. Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, Bassetti CL, Vos T, Feigin VL. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. Lancet Public Health. 2020. 5:e551-e567.

Figure 2. Dementia Friendly Wyoming, Types of Dementia,

Figure 3. BioRender (2022) "Neural Stem Cell Differentiation"

Figure 4. Image self-produced in Biorender.com.

Figure 5. Figure comes from Internet; MOCA test pdf.

Figure 6. Proposed mechanisms for the role of apolipoprotein (ApoE) in AD pathogenesis. No changes have been made to the figure; License Number 4278980016081.
(Maria Paraskevaidi, Pierre L. Martin-Hirsch, and Francis L. Martin. Progress and Challenges in the Diagnosis of Dementia: A Critical Review)

Figure 7. BioRender (2019). Pathology of Alzheimer's Disease 2.

Figure 8. OECD/WHO (2023), Step Up! *Tackling the Burden of Insufficient Physical Activity in Europe,* OECD Publishing, Paris

Figure 9. Burtscher, J.; Millet, G.P.; Place, N.; Kayser, B.; Zanou, N. The Muscle-Brain Axis and Neurodegenerative Diseases: The Key Role of Mitochondria in Exercise-Induced Neuroprotection. Int. J. Mol. Sci. 2021, 22, 6479

Figure 10. Madhu LN, Somayaji Y, Shetty AK. Promise of irisin to attenuate cognitive dysfunction in aging and Alzheimer's disease. Ageing Res Rev. 2022 Jun;78:101637. Epub 2022 Apr 30. PMID: 35504553; PMCID: PMC9844023.