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The multifactorial nature of healthy brain ageing: Brain changes, functional decline and protective factors

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1 **Abstract**

2 As the global population faces a progressive shift towards a higher median age, understanding the
3 mechanisms underlying healthy brain ageing has become of paramount importance for the preservation of
4 cognitive abilities. The first part of the present review aims to provide a comprehensive look at the
5 anatomical changes the healthy brain endures with advanced age, while also summarizing up to date
6 findings on modifiable risk factors to support a healthy ageing process. Subsequently, we describe the
7 typical cognitive profile displayed by healthy older adults, conceptualizing the well-established age-related
8 decline as an impairment of four main cognitive factors and relating them to their neural substrate
9 previously described; different cognitive trajectories displayed by typical Alzheimer’s Disease patients and
10 successful agers with a high cognitive reserve are discussed. Finally, potential effective interventions and
11 protective strategies to promote cognitive reserve and defer cognitive decline are reviewed and proposed.

12

13

14 1. Introduction – Defining Healthy Brain Ageing

15 The past 250 years have seen a steady increase in the average human life expectancy and, although this
16 trajectory has been temporarily altered by the recent Covid-19 pandemic¹, this trend is projected to
17 continue in the coming years in most industrialized countries². This notion is a compelling call to address
18 the issue of promoting and supporting a healthy ageing process. Indeed, a lengthening lifespan does not
19 necessarily align with an equally prolonged healthspan³, defined as the average length of a healthy life.
20 Postponing the onset and attenuating the severity of late-life morbidity, aptly defined as ‘compression of
21 morbidity’⁴, has subsequently become a health priority.

22 The World Health Organisation (WHO) defines healthy ageing as “the process of developing and
23 maintaining the functional ability that enables wellbeing in older age”⁵. Therefore, the WHO’s definition
24 emphasizes that a healthy ageing trajectory is a ‘process’, a goal achieved throughout the lifespan to ensure
25 the best possible outcome for one’s later years. The definition relies on the concept of ‘functional ability’,
26 qualified as “having the capabilities that enable all people to be and do what they have reason to value”.
27 This notion epitomizes the influential model proposed 25 years ago by Rowe and Kahn⁶, which lists three
28 main components of successful ageing: maintenance of physical and cognitive function, minimised risk of
29 disability and continued engagement with life.

30 Embracing this framework, a significant spotlight should be afforded to healthy brain ageing. Seminal
31 studies tackling the topic of ageing have traditionally focussed on cognitively disabled older individuals⁷
32 and, more recently, individuals displaying extraordinarily positive ageing outcomes (so called super-
33 agers)^{8,9}. The present review, instead, concentrates on usual healthy brain ageing⁷, which we define as the
34 composite pattern of modifications the human brain physiologically endures with advancing age, from the
35 anatomical, functional and cognitive standpoint, when adequate typical functional ability and adaptability
36 are retained.

37 The first portion of our descriptive review will provide a synopsis of the anatomical transformations
38 observed in the brain with advanced age, while also summarizing current findings on modifiable risk
39 factors. Subsequently, we will relate these neural substrate modifications with the associated typical
40 cognitive decline profile displayed by older individuals¹⁰ and propose potential beneficial active
41 interventions to support cognitive reserve¹¹, a mitigating factor preventing pathologic decline discussed in
42 Paragraph 6.

43 2. Structural changes associated with healthy brain ageing.

44 Ageing physiologically causes a whole host of anatomical and functional modifications in the brain, ranging
45 from the intracellular to macrostructural¹² levels. For the scope of this narrative review, we will discuss
46 these changes in terms of microscale (i.e., intracellular), mesoscale (i.e., intercellular or local circuitry) and
47 macroscale (i.e., whole brain, large scale networks) changes (Figure 1). However, it is important to note
48 that we are not implying that these three levels are separate, nor that they should be studied as such.
49 Indeed, they are better understood as an interconnected and mutually influential continuum.

50 2a. Predisposing genotypes

51 Several studies have investigated the heritability of longevity, estimating that around 25% of the variation
52 in lifespan is caused by genetic differences¹³; similar efforts have been made to estimate the heritability of
53 healthy cognitive ageing^{14–18}. A meta-analysis of genome-wide association studies of 31 cohorts,
54 considering a total sample size of almost 54 thousand healthy individuals, found a significant relationship
55 between general cognitive function and four genes known to be related to the development of Alzheimer’s
56 disease (TOMM40, APOE, ABCG1 and MEF2C)¹⁶. Among them, the APOE e4 genotype was found by later
57 studies to predict steeper cognitive decline in older adults even when not affected by Alzheimer’s^{18–21}. The

58 meta-analysis results indicate a polygenic model of inheritance¹⁶; in recent years the calculation of
59 polygenic scores (PGS) has become common in research aiming to investigate genetic predictors of disease,
60 health or, more generally, traits²². PGSs are extracted from published genome-wide association studies
61 that have tested the correlation of millions of single-nucleotide polymorphisms with specific phenotypes
62 (e.g., disease, educational attainment...); scores can then be computed on any individual genotype to
63 measure the genetic probability of specific traits or the liability to a specific disease. However, although
64 PGSs were found to predict cognitive performance across several domains in old age, evidence of their
65 effectiveness in predicting cognitive decline is still lacking¹⁸.

66 ----- Please insert Figure 1 near here -----

67 **2b. The Micro scale**

68 A prominent review published almost ten years ago narrowed down the complex biology of ageing by
69 identifying nine hallmarks of it²³, which represent widely investigated common denominators of the ageing
70 process²⁴: genomic instability, telomere attrition, epigenetic alterations, cellular senescence, altered
71 intercellular communication, loss of proteostasis, stem cell exhaustion, deregulated nutrient sensing and
72 mitochondrial dysfunction. These hallmarks are integrated, co-occurring and mutually causing one another,
73 and can be adopted as a roadmap to discuss the microscale level changes occurring in the ageing brain.

74 DNA damage is considered among the primary²³ hallmarks of ageing, initiating a signalling cascade that
75 reverberates through cells, driving them into apoptosis or senescence to avoid the replication of damaged
76 genetic information^{24,25}. **Genomic instability** is the increased tendency of the DNA to mutate, in response to
77 both exogenous and endogenous factors, and the subsequent accumulation of genetic damage²³. Even
78 under physiological conditions, the DNA is not chemically stable²⁶; additionally, it is vulnerable to chemical
79 attacks by agents such as reactive oxygen species, resulting in prominent oxidative stress and consequent
80 high levels of DNA mutations recorded in advanced age^{25,27}. Indeed, older brain tissue presents increased
81 DNA deletions rates (the removal of at least one nucleotide in a gene during DNA copying) and reduced
82 ability for DNA repair^{12,28}. Although spontaneous DNA damage occurs randomly in all cell types on the order
83 of tens of thousands of times per day²⁶, some chromosomal regions are more prone to age-induced
84 deterioration, such as telomeres, the terminal ends of DNA molecules²⁹. Most mammalian cells do not
85 express telomerase, the enzyme responsible for the replication of telomeres³⁰; this results in **telomere**
86 **attrition**, the physiological gradual and cumulative loss of chromosomes' ends protective caps during DNA
87 replication²⁹. Telomere attrition limits the overall number of times any cell can replicate, slowly leading to
88 cell loss in all organs with advancing age; thus, telomere attrition has been studied as a biomarker of brain
89 age^{24,31}. Notably, promising genetic interventions are being studied in animal models, and indicate that
90 premature ageing can be reverted in mice through telomerase reactivation³².

91 A further aspect of genomic instability are **epigenetic alterations**³³. Epigenetic mechanisms regulate gene
92 expression by changing the chemical structure of the DNA without affecting its coding sequence; epigenetic
93 alterations consist of either the addition/removal of methyl groups from DNA (DNA methylation) or of
94 changes to the histones, proteins that bind to DNA molecules in chromosomes (PARylation and acetylation
95 of DNA and histones)^{12,24,34}. Epigenetic mechanisms determine both the development and the
96 deterioration of brain tissues (see here³⁴ for a review on epigenetics in neurodegeneration and
97 neuroprotection) and are crucial for higher cognitive functions (e.g., memory)³⁵. Multiple lines of evidence
98 suggest that ageing is accompanied by epigenetic changes²³; epigenetic clocks, thought to capture
99 molecular ageing, are among the best-studied ageing biomarkers^{36,37}.

100 DNA damage too extensive to be quickly repaired induces signalling events that can result in senescence,
101 which plays a causal role in ageing²⁵. **Cellular senescence** is a stable arrest of the cell cycle, an adaptive
102 mechanism by which the organism prevents the proliferation of damaged genetic material. Due to the
103 phenomenon of 'contagious ageing', senescent cells induce senescence in neighbouring ones. The increase

104 in senescent cells generation, coupled with their deficient clearance results in their deleterious
105 accumulation²³. Because senescent cells secrete high levels of proinflammatory cytokines³⁸, cellular
106 senescence contributes to inflammation. Tissue inflammation is so typical of ageing that the term
107 ‘inflammageing’ was coined³⁹, and upregulated **neuroinflammation** studied as a marker of brain age²⁴.
108 Multiple other causes concur to the chronic inflammatory state observed in the ageing brain, such as
109 invading pathogens, the accumulation of damaged tissue, neuronal injury, a decrease in the immune
110 system efficacy¹², the occurrence of improper autophagy⁴⁰, and **loss of proteostasis** (i.e., the balance
111 between protein synthesis, folding, trafficking, aggregation, disaggregation, and degradation)⁴¹. The
112 proteostasis network becomes increasingly less efficient with age⁴², and the subsequent deposition of
113 proteins is among the best-known correlates of normal ageing⁴³. A recent review of proteomic studies has
114 identified over a thousand proteins that, across the whole human organism, including the brain, undergo
115 modifications with age and are relevant to ageing and age-related disease⁴⁴. Thus, proteomic clocks could
116 be implemented and serve a similar purpose to epigenetic clocks³⁶.

117 Neuroinflammation is initiated by microglia, the immune cells in the central nervous system and primary
118 source of proinflammatory cytokines. Under non-damaged conditions, microglia are physiologically in a
119 homeostatic “resting” state; they become activated in response to exposure to pathogen-associated or
120 damage-associated molecular patterns⁴⁵. While microglia cells have a neuroprotective role in the young
121 brain, multiple studies have shown that they gradually transition to a chronically activated and neurotoxic
122 state in older adults⁴⁶, irrespective of their cognitive status^{47,48}. Pathological **microglia activation** is believed
123 to promote neurodegeneration⁴⁶ and an experimental intervention based on the induction of high
124 frequency activity in the gamma frequency band has proven effective in modifying microglia, reducing
125 inflammation and improving protein clearance⁴⁹.

126 To counteract tissue inflammation, the use of stem cells has been proposed⁵⁰. The role of stem cells in
127 healthy ageing⁵¹ has been at the forefront of the scientific debate for a number of years, and exhaustively
128 discussing it is beyond the scope of this review. Stem cells have been found in most tissues and organs in
129 adult humans including, notably, the brain⁵². A stable populations of proliferating stem cells is necessary to
130 the ability of tissues to recover from damage; however, with advanced age the number and proliferative
131 capacity of stem cells decline, a phenomenon called **stem cell exhaustion**^{24,29,51}.

132 Neuroinflammation is one of the most important **alterations in intercellular signalling** related to ageing. A
133 second one is **deregulated nutrient sensing**²³, which alters the metabolism and plays a critical role in the
134 ageing process⁵³. Nutrient sensing is the ability of all cells, including neurons, to recognize nutrient levels
135 within them and in the bloodstream and respond accordingly by absorbing, storing and converting
136 nutrients to ensure energy provision and maintain blood nutrient levels within safe ranges (e.g., blood
137 sugar levels). A wide range of nutrient signalling pathways, especially those involving insulin, are
138 deregulated in ageing⁵⁴. Excessive activation of nutrient-signalling pathways has been linked with negative
139 ageing outcomes: genotypes that determine a lowered activity of nutrient-signalling pathways are also
140 predictive of successful ageing⁵⁵ and calorie restrictive diets, which downregulate nutrient signalling, have
141 well-established neuroprotective effects⁵⁶.

142 One further source of metabolism imbalance in ageing is **mitochondrial dysfunction**⁵³. With advancing age,
143 the efficacy of the respiratory chain dwindles, reducing ATP generation⁵⁷; this phenomenon is particularly
144 relevant in brain cells, as neurons are highly metabolically active⁵⁸. Although the link between
145 mitochondrial dysfunction and ageing has not been fully elucidated yet, it is known that in the elderly brain
146 damaged mitochondria overproduce reactive oxygen species²⁴, adding to the oxidative damage of DNA and
147 aggravating genomic instability. Among its consequences, persistent DNA damage depletes the coenzyme
148 NAD⁺⁵⁹; indeed, an age-dependent reduction of NAD⁺ has been demonstrated in healthy humans⁶⁰. NAD⁺ is
149 an oxidation-reduction factor essential to energy metabolism and mitochondrial homeostasis⁵⁹ so that its

150 depletion further aggravates mitochondrial dysfunction, in a detrimental loop that contributes to the
151 ageing process.

152 **2c. The Meso scale**

153 Age-driven mesoscale modifications (i.e., impacting the intercellular or local circuitry level) are among the
154 most studied phenomena concerning the ageing brain. The best known of them is the formation of
155 **neurofibrillary tangles** (NFT) and **amyloid plaques** (AP), a firmly established characteristic of brains
156 affected by dementia of the Alzheimer's type which is also observed in healthy ageing^{12,43}. Neurofibrillary
157 tangles form in the intracellular space; they are insoluble twisted fibres made mostly of tau protein, an
158 essential building block of the microtubular structure that allows intracellular molecular transport. Amyloid
159 plaques, instead, accumulate in the extracellular space; while protein fragments (i.e., amyloids) are broken
160 down and removed in the healthy young brain, ageing causes protein clearance to decline, resulting in the
161 accumulation of hard insoluble plaques of protein fragments between neurons^{41,43}. On the one hand, the
162 pathological misfolding of tau protein impacts the microtubule structures, which collapse and disrupt the
163 intracellular trafficking of materials; on the other, plaques around nerve cells induce their death,
164 conceivably by triggering an immune response. Thus, AP and NFT lead to **local hypoactivation and**
165 **atrophy**⁶¹ in older brains. Although manifesting on different timescales⁶², atrophy is observed across
166 different multimodal associative brain regions, particularly the medial temporal and parietal cortex⁶³.
167 Because episodic memory loss is among the cognitive functions most susceptible to ageing, **medial**
168 **temporal (i.e., hippocampal, entorhinal and parahippocampal) grey matter atrophy**⁶⁴ and
169 hypoactivation⁶⁵ have been especially extensively studied and reported.

170 The **cerebrovascular system** is impacted by age. Vessels tend to diminish in size^{12,66,67}, capillaries to reduce
171 in number⁶⁸ and microbleeds and small infarctions are common⁶⁹ with advanced age, causing overall
172 decreases in cerebral perfusion: blood flow to both the grey and white matter lowers by an estimated 0.5%
173 every year from early adulthood onwards⁷⁰. Cerebrovascular causes have been indicated for the **white**
174 **matter lesions** commonly observed in ageing¹²: an age-related loss of myelinated axons⁷¹ and a decline in
175 fractional anisotropy⁷² have been observed; the periventricular and deep subcortical white matter lesions
176 in particular are thought to likely arise as a result of hypoperfusion and microvascular disease^{68,73,74}.

177 Intercellular communication impairment is one of the hallmarks of ageing discussed in the previous section
178 with regards to inflammageing and deregulated nutrient sensing. At the larger neural population scale,
179 intercellular communication is impaired by **neurotransmitter imbalances**. Most neurotransmitters show
180 decrements with age (e.g. dopamine and serotonin⁶³) with cascade effects on cognitive function;
181 GABAergic and glutamate dysregulation⁷⁵ are of particular interest because of their implication in **brain**
182 **plasticity**⁷⁶ and on **local oscillatory activity changes**. EEG and MEG studies found that healthy ageing is
183 characterized by changes in several metrics of resting state oscillatory activity (frequency, power,
184 morphology and distribution). Background oscillatory activity tends to slow down in the elderly, with the
185 alpha rhythm (8-13 Hz) becoming dominant, and an increase in delta (0.1-4 Hz) and theta (4-8 Hz) power
186 with respect to young adults⁷⁷; this is coupled with decreased activity in the gamma frequency band (30-80
187 Hz)⁷⁸. The decrease in oscillatory activity in the gamma band is particularly interesting; previous studies
188 have tied local activation in the gamma frequency band to peri-somatic inhibition⁷⁹, which relies on the
189 activation of Parvalbumin-positive intracortical inhibitory GABAergic nets whose dysfunction accounts for
190 the reduction in gamma power observed in the elderly⁸⁰. Moreover, their impairment leads to aberrant
191 modulation of intrinsic neuronal excitability and, subsequently, aberrant neuronal plasticity⁸¹. Indeed, local
192 mechanisms of brain plasticity, and particularly synaptic plasticity^{82,83}, are impaired in the ageing brain^{84,85}.

193 **2d. The Macro scale**

194 On a macroscale level (i.e., whole brain, large scale networks), the modifications that impact the brain
195 during ageing are well characterized, and the relevance of these changes on cognitive functions is widely
196 recognized in the scientific literature.

197 Recently, a brain-wide cerebrospinal fluid and interstitial fluid drainage pathway was characterized, the
198 glymphatic system. The glial-lymphatic system of vessels channels extracellular fluid within the central
199 nervous system to clear interstitial metabolic waste from the brain parenchyma; recent evidence suggests
200 that ageing leads to an **abnormal glymphatic function**⁸⁶, which results in the accumulation of metabolic
201 waste in the extracellular space, such as amyloid fragments which, as discussed in paragraph 2c, contribute
202 to neuronal death and cortical atrophy (for a review see⁸⁷).

203 As discussed in the previous paragraph, cellular loss and **widespread hypoperfusion**^{70,88} result in local
204 atrophy⁶¹ across the entire brain; therefore, an overall **decrease in cortical volume and thickness** is
205 observed in older individuals. A recent study, which pooled structural MRIs of more than 100,000 human
206 participants, measured brain volumes during the lifespan and found that both grey and white matter
207 volumes decline over time, with steeper declines for the grey matter⁸⁹, accompanied by an increase in
208 ventricular size and cerebrospinal fluid volume⁸⁹. Cortical atrophy is particularly interesting because of its
209 strong correlation with cognitive performance⁹⁰.

210 Moreover, whole-brain structural and functional connectivity are similarly and coherently impacted by
211 ageing⁹¹. Findings on structural metrics consistently describe **widespread decreases in fractional**
212 **anisotropy** in older compared to younger adults^{72,91,92} and age-related reduction in structural connectivity
213 and efficiency starting from early adulthood^{93,94}. Studies focussing on functional connectivity also report
214 age-related modifications: first, the ageing brain is characterized by **within network effects**, i.e., alterations
215 of synchronized activity between nodes of cortical networks. Key brain networks such as the default mode
216 network (DMN), the frontoparietal network (FPN) and the salience network (SN) all show a **decreased**
217 **within network connectivity** in the elderly⁹⁵⁻⁹⁸. Second, between-network effects have been found in
218 normal ageing. These include **increased between network-connectivity** (i.e., increased positive correlations
219 between networks that are not typically coupled and decreased anticorrelations between networks)^{91,99}.
220 This has been interpreted as a loss of functional system segregation between large-scale networks
221 subserving cognition and it may potentially reflect an over-recruitment compensatory strategy^{91,100,101}. It is
222 worth noting that functional connectivity studies systematically measuring its changes during the lifespan
223 are still scarce and not always consistent in their results¹⁰². Recent systematic reviews and meta-analyses
224 have validated the findings described above, especially confirming the reported disruption of within
225 network connectivity in the DMN¹⁰³ and reduced network-to-network segregation⁹⁹, but further second
226 level evidence is still needed.

227 3. Modifiable risk factors

228 Based on the most recent report from the Lancet commission on dementia prevention, twelve modifiable
229 risk factors have been identified which might delay or avoid dementia and promote healthy ageing:
230 excessive alcohol consumption, history of traumatic brain injury (TBI), exposure to air pollution, lower
231 education level, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity,
232 diabetes and infrequent social contact¹⁰⁴. After reviewing the available literature, we propose two
233 additional modifiable risk factors: high stress exposure and sleep fragmentation/sleep disorders (Figure 1,
234 top arrow). In this revised framework, we included depression into the broader construct of negative
235 psychological traits. Furthermore, we integrate low education level into the wider concept of cognitive
236 reserve¹⁰⁵, which is also related to IQ, occupational attainment, physical fitness, and several other lifelong
237 exposures discussed in paragraph 6.

238 Some authors propose that several risk factors for cognitive decline could be traced to low socioeconomic
239 status¹⁰⁶. For example, low income is associated with worse eating habits¹⁰⁷, increased rate of school

240 dropout¹⁰⁸, a higher probability of living in densely polluted areas¹⁰⁹ and diminished life expectancy¹¹⁰. A
 241 recent longitudinal study found that lower wealth predicts a steeper decline in physical, sensory and
 242 cognitive health, as well as in emotional well-being¹¹¹. In the United States, such factors are inextricably
 243 linked to disparities in health care delivery and economic status in racial and ethnic minorities^{112,113}.
 244 Therefore, when considering risk and protective factors to improve healthy ageing in the whole population,
 245 bridging disparities in social and racial inequalities must be considered.

246 The analysis of predisposing risk factors and beneficial interventions protecting from cognitive decline is for
 247 the most part based on observational studies; although the preferred research design, at least for
 248 interventions, would be a randomized clinical trial (RCT), it is often complex to build a study to be able to
 249 evaluate them in trials (e.g., educational attainment, lifelong physical fitness exercise). This can impact the
 250 quality of the available evidence on predisposing risk factors and beneficial interventions, which is
 251 sometimes low²⁰. Because study designs are mainly limited to observational designs, improvements in
 252 research methods are needed, such as better validated standardized metrics of cognitive decline and
 253 exposure to risk/protective factors, as well as confirmatory second level evidence.

| Risk Factor | Level | Evidence |
|--|--------------|---|
| <i>Air Pollution</i> | Micro | Animal models suggest airborne particulate pollutants accelerate neurodegenerative processes through cerebrovascular and cardiovascular disease, A β deposition, and amyloid precursor protein processing ¹⁰⁴ . A systematic review including 13 longitudinal studies found that exposure to air pollutants was associated with increased dementia risk ¹¹⁴ . |
| <i>Smoking</i> | Micro | Different systematic reviews confirm that active smoking increases the risk of dementia ^{20,115} . Indeed, smoking increases oxidative stress and is a risk factor for multiple vascular conditions (e.g., high blood pressure, high cholesterol) as well as for insomnia and sleep apnea, all linked to an increased probability of pathological cognitive decline. |
| <i>History of TBI</i> | Micro | Evidence indicates that even one single severe TBI is associated in both humans and mouse models with widespread hyperphosphorylated tau pathology ¹⁰⁴ . Multiple studies and meta-analyses have confirmed that a history of TBI increases the risk of dementia ^{116,117} , even reporting a two-fold surge ¹¹⁷ . It is worth noting that data from the National Alzheimer's disease Coordinating Center database suggest that the clinical profiles of older adults with and without a history of TBI differ significantly and can be distinguished, suggesting that TBI is not necessarily just a risk factor for other known dementia subtypes, but rather that TBI-induced dementia should be considered a subtype of his own ¹¹⁸ . |
| <i>Sleep fragmentation/Sleep disorders</i> | Micro | Insomnia is associated with increased AD risk, while Sleep disordered Breathing correlates with a higher incidence of all-cause dementia ¹¹⁹ . Because of the critical role afforded to sleep in protein and neurotoxic waste clearance ¹²⁰ , the primary proposed pathway revolves around diminished protein clearance function and subsequent pathological accumulation ¹²¹ . |
| <i>Obesity/weight</i> | Micro/Meso | Metabolic morbidity accelerates most of the hallmarks of brain ageing (e.g., neuroinflammation, impaired neuronal homeostasis) ⁵⁶ . Moreover, studies have documented reduced grey matter volume ¹²² and white matter integrity ¹²³ in multiple brain regions and reduced functional connectivity ¹²⁴ in obese individuals. |
| <i>Chronic Stress</i> | Micro / Meso | Chronic stress leads to the secretion of glucocorticoids, such as cortisol, whose excessive level is harmful to brain structures; research |

| | | |
|--------------------------------------|------------|---|
| | | <p>has especially focussed on the deleterious effects of stress on the hippocampal formation. Animal studies found that stress impairs hippocampal synaptic plasticity and neuronal proliferation, resulting in hippocampal atrophy¹²⁵. In humans, high stress levels were found to be associated with increased neural inflammation and diminished immune responses¹²⁶ as well as decreased brain volume and more prominent white matter lesions¹²⁷.</p> <p>In contrast hormesis, i.e., the steady prolonged exposure to mild levels of stress, increases stress resilience and reduces vulnerability, with positive effects on cognitive ageing¹²⁶.</p> |
| <i>Diabetes</i> | Micro/Meso | Diabetes leads to vascular pathology ¹²⁸ and to reduced hippocampal neurogenesis and neuroplasticity ¹²⁹ . A systematic review of observational studies totalling a sample size of over 32 thousand individuals has confirmed the increased risk of cognitive decline in diabetic patients ²⁰ . |
| <i>Hearing impairment</i> | Meso | A US prospective cohort study of 194 adults found that midlife hearing impairment is associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal cortex ¹³⁰ . |
| <i>Excessive Alcohol consumption</i> | Meso/Macro | According to the UK Whitehall study, with 23 years follow-up, drinking more than 14 alcohol units per week is associated with right-sided hippocampal atrophy ¹³¹ and increased dementia risk. Moreover, alcohol consumption is linearly negatively associated with grey and white matter volume ¹³² , so that high alcohol consumption correlates with increased atrophy. |
| <i>Physical inactivity</i> | Meso/Macro | Exercise yields an increase in brain plasticity, indexed by heightened BDNF concentration, and has a protective role against brain volume loss and AD pathology, as well as cardiovascular pathologies, that are risk factors for dementia ¹²⁷ . |
| <i>Hypertension</i> | Meso/Macro | Midlife hypertension is associated with reduced brain volumes and increased white matter hyperintensity volume ¹⁰⁴ . |
| <i>Negative Psychological Traits</i> | Macro | Psychological and personality attributes such as optimism, positivity, and a sense of purpose have been associated with healthy ageing. One review reported that both early and late-life depression correlate with increased in dementia risk ^{20,133} . Proposed pathways include the direct effects of depression on stress hormones, neuronal growth factors and hippocampal atrophy ¹³⁴ . |
| <i>Social isolation</i> | Macro | Low social interaction is associated with increased stress, disrupted sleep patterns and inflammation, leading to more prominent AD brain pathology and steeper rates of brain volume loss ¹²⁷ . Additionally, social contact enhances cognitive reserve by encouraging beneficial behaviours (e.g., physical activity, cognitive stimulation). |
| <i>Low Cognitive Reserve</i> | Macro | Individuals with higher Cognitive Reserve display lower task related cortical activation, more robust connectivity in key brain networks, and a better compensatory activation in response to ageing and pathology ^{105,135,136} . Additionally, higher cognitive activity levels, especially in early life and in middle age, correlate with decreased A β deposition ¹²⁷ . |

254 Table 1 - Modifiable risk factors impacting healthy brain ageing.

255 ----- Please insert Figure 2 near here -----

256 **4a. Cognitive hallmarks of healthy ageing**

257 The physiological brain changes associated with age, described in paragraphs 2b, 2c and 2d, are
258 accompanied by a typical decline in cognitive functions, which follow different trajectories¹³⁷ (Figure 2a).
259 Note that the profile described here is a correlate of normal ageing, rather than a pathological outcome: it
260 represents a natural decay in cognitive functions, similar to expected declines in physical functioning that
261 accompany normal ageing. As such, the cognitive declines outlined here do not prohibit functional
262 independence, particularly when compensatory strategies are engaged.

263 When reviewing the literature on the cognitive correlates of ageing, it is necessary to consider some
264 methodological issues. Ageing cognitive trajectories can be studied adopting cross-sectional or longitudinal
265 study designs, whose findings can sometimes be inconsistent. Inconsistencies can be ascribed, on the one
266 hand, to cross-sectional study designs being flawed by well documented biases and inferential problems
267 such as cohort effects, resulting in inappropriate estimations of the effect of age on cognition during the
268 lifespan^{138–142}. However, on the other hand, they could be due to longitudinal study designs presenting retest
269 or practice effects; positive gains due to retest have been reported even when time intervals are of
270 considerable magnitude (above 5 years)^{143,144}, and could therefore be very complex to minimize in
271 longitudinal study designs. Moreover, previous evidence indicates retest effects to have a rather large
272 positive effect size, potentially masking age-related decline^{144–146} and, critically, that it is hard to build a
273 statistical model to effectively control for retest effects¹⁴⁷. Based on these considerations on the impact of
274 cohort and retest/practice effects, we included in the literature informing this section of the review on
275 cognitive ageing both longitudinal and cross-sectional evidence with large sample sizes, and report findings
276 with convergent support in both kinds of study designs.

277 Cognitive functions broadly follow three patterns of age-related change: some decline across the lifespan,
278 some in late-life, and others are relatively stable, or even moderately increase over time¹³⁷. Performance in
279 life-long declining cognitive abilities decreases from its peak throughout the adult lifespan. The hallmark of
280 cognitive ageing is decreased processing speed, which slowly declines in early adulthood and linearly
281 recedes after age 40^{148–150}. Similarly, working memory performance also linearly declines, both in its
282 visuospatial and in its verbal components^{151–153}. Critically, and in part due to the deterioration of working
283 memory abilities, memory encoding abilities also decline from a very young age, resulting in worsened
284 performance both in long term^{148,152,154–156} and short-term memory^{157,158} tasks.

285 Most cognitive functions, however, experience only slight declines until later in life. Numerical ability,
286 measured through mathematical tests, is stable until one's mid-fifties¹⁴⁸. Spatial orientation seems to
287 slightly increase until age 30¹⁴⁸, then plateaus and only declines after one's sixties^{154,159}. A similar pattern
288 has been reported for reasoning abilities, which undergo a significant decline after the age of 50^{148,151,154,160}.
289 Shifting (i.e. mental set shifting) and inhibition abilities (i.e. inhibition of prepotent responses)¹⁶¹ also
290 display a late-life decrease^{150,154}: performance steeply declines after 50 and 70 years of age, respectively.
291 These late-life declining abilities are the ones most affected by discrepancies in results between
292 longitudinal and cross-sectional measurements; indeed, although cross-sectional estimates demonstrate
293 clear declines in spatial orientation and reasoning with ageing, longitudinal assessments support a
294 maintenance of these functions at the individual level¹⁴⁵.

295 Cognitive functions which remain stable in life have been termed "crystallized intelligence"¹⁴⁹. Semantic
296 knowledge is one of them, increasing until the mid-fifties and only slightly lowering after age 70^{148,154–157,159}.
297 Emotional regulation and processing seem to be maintained, or even improved, with age: for instance,
298 performance in theory of mind tasks which require the attribution of mental states to others remains
299 intact¹⁶², and data suggests that the elderly attend to the emotional content of memories more than young
300 adults do^{137,163}. Although the most characteristic and recognisable symptom of old age is memory loss, not
301 all memory functions decline with age. Autobiographical memory is largely preserved¹⁶⁴, especially for
302 events occurring in young adulthood (for a review see¹⁶⁵). Automatic memory, measured as the magnitude
303 of priming effects, seems to remain intact until late age as well^{156,166}.

304 Declining and stable cognitive functions are broadly referred to as fluid and crystallized, respectively¹⁴⁹, and
305 it has been put forth that fluid declines might be compensated for by retained crystallized abilities.
306 According to the 'dedifferentiation hypothesis', however, all abilities deteriorate after the age of 85,
307 potentially because of vision and hearing loss¹⁶⁷; however, this generalized decline has not been
308 consistently confirmed¹⁶⁸. Moreover, recent studies have moved past this classical distinction and reported
309 that, although they diverge in the steepness of their decline, rates of change correlate across all cognitive
310 domains, so that individuals with greater losses in fluid abilities also display smaller gains, or even losses, in
311 crystallized abilities^{169,170}.

312 **4b. The four components of cognitive decline**

313 The profile of physiological cognitive decline described in paragraph 4a can be characterized with a four-
314 factor model (Figure 2C). Previous studies that have applied latent component analyses to both longitudinal
315 ¹⁷¹ and cross-sectional data¹⁶⁰ report that, although the bulk of individual differences in cognitive decline
316 can be attributed to domain general processes, a significant amount of it is accounted for by four distinct
317 domains: processing speed, memory, reasoning and visuospatial function.

318 **Processing speed**, i.e. the ability to carry out mental operations quickly and efficiently, has been proposed
319 as the prime indicator of cognitive ageing and the driving cause of other impairment¹⁷². Interestingly,
320 however, some studies suggest that the impairment in other cognitive tests, especially memory and
321 reasoning, emerges sooner in life than processing speed deficits^{145,148,151}; yet, this could be accounted for by
322 the fact that pure processing speed tests (e.g., letter or pattern comparison, finding A's) are very simple,
323 and may be prone to ceiling effects. Because processing speed is known to heavily rely on general white
324 matter integrity¹⁷³, interventions known to promote its health, such as physical activity¹⁷⁴, might be
325 beneficial, as reported by a meta-analysis of randomized clinical trials on the effect of aerobic exercise
326 training, which found it to be associated with improvements in processing speed¹⁷⁵.

327 **Declarative memory**, i.e. the ability to retrieve and state previously encoded information after a brief
328 (short term memory) or long (long term memory) time interval, is notoriously linked to the activity and
329 integrity of medial-temporal structures, which are essential nodes of the DMN. Although research on the
330 definitive benefits of memory training is still underway¹⁷⁶, promising results hint that mnemonic stimulation
331 could be a tool for long time memory maintenance¹⁷⁷.

332 The aforementioned studies that have investigated latent components of cognitive decline^{160,171} include
333 visuospatial function, i.e. the ability to mentally rotate 2D and 3D patterns, as one of their components. In
334 the present review, we revisit this concept in light of novel findings that tightly link this capacity with
335 numerical abilities¹⁷⁸. Although they are two separate functions, **numeric and spatial abilities** rely on the
336 same neural substrate, centred around the frontoparietal network¹⁷⁹, which can be preserved and
337 enhanced through cognitive training^{149,180,181}.

338
339 **Reasoning** requires a complex and composite definition: it is the ability to divergently think, make use of
340 unfamiliar information, identify relations, form concepts and draw inferences¹⁷¹. However, taking into
341 consideration the overlapping neural substrates underlying these processes¹⁸², we believe reasoning
342 comprises the three "frontal lobe" executive functions: mental set shifting ('Shifting'), information updating
343 and monitoring ('Working Memory'), and inhibition of prepotent responses ('Inhibition')¹⁶¹. This high-order
344 reasoning factor has widespread neural bases, which mainly rely on the dorsal attention network, and to a
345 lesser extent on both the left and right fronto-parietal control networks^{183,184}. Reasoning abilities, too,
346 draw positive benefits from cognitive training^{149,180,181}.

347 **5. Entering the era of personalized brain health tracking**

348 In light of the critical relevance of implementing any intervention with prompt timing, the issue of tracking
349 brain and cognitive health is pivotal. A new wave of technological progress is opening the stimulating

350 prospect of designing innovative tools to measure and track health daily, increasing the temporal resolution
351 of traditional cognitive check-ups and giving access to an abundance of digital biometric measures so far
352 undetected¹⁸⁵.

353 Shifting from pen and paper cognitive assessment and stimulation tools to computerized methods, besides
354 potentially yielding better results¹⁸⁶ because of the increased interactive engagement, allows for the
355 collection of more informative data. Eye-tracking technologies to assess dynamic vision and measure
356 attention allocation through recording of fixation and saccades¹⁸⁷, biomarkers derived from human voice¹⁸⁸,
357 the use of wearables such as actigraphs to track sleep and other health parameters¹⁸⁹ and the recording of
358 pen pressure or speed in drawing and writing tasks¹⁹⁰ are all examples of viable metrics and potential
359 proxies of general health and cognitive functioning; their application to tracking healthy brain ageing may
360 become a key component of health monitoring .

361 **6. From structural to cognitive: how well can the brain adjust to change?**

362 Brain age may or may not align with chronological age, but it can be estimated by measuring structural and
363 functional brain markers³⁶. This roughly falls within the ambit of estimating one's brain reserve, defined as
364 the 'neurobiological capital', or the quantifiable brain resources (e.g., synaptic count, intracranial volume,
365 white and grey matter integrity) necessary to maintain adequate function¹⁹¹. The extent to which individual
366 brains preserve their neurochemical, structural and functional integrity, at micro, meso and macro-scale
367 levels, has also been referred to as "brain maintenance" in longitudinal studies¹⁹².

368 The concept of brain maintenance implies that variations in structural characteristics would tightly
369 correspond to a better cognitive performance. However, this is not always the case^{193,194}, as certain
370 individuals display better coping abilities and mitigate the cognitive decline which would be expected based
371 on their underlying brain damage. This raises the question of how to bridge the gap between one's brain
372 structure, brain function and metrics of cognition. The construct of cognitive reserve (CR) was put forward
373 as a moderator between brain pathology and its clinical outcome^{11,105}. While brain reserve is a passive
374 protective factor, based on the sheer amount of expendable substrate, CR is conceptualized as the brain's
375 active coping in response to damage, through compensatory or pre-existing cognitive processing¹⁹⁵.
376 Although potentially influenced by common lifestyle factors, cognitive reserve and brain
377 maintenance/reserve are two separate, uncorrelated processes¹⁹⁶.

378 One major hurdle to the research on CR is its measurement, which is to this day uneven across studies. The
379 most frequently adopted proxy of CR is years of education^{193,197,198}; however, high education alone is
380 arguably a reductive index for this broader construct. Indeed, while it is true that individuals with higher
381 education have higher scores in all cognitive domains, evidence casts doubt on the notion that high
382 education per sé is a predictor of slower cognitive decay rates, as multiple studies on large sample sizes
383 have reported no difference between the decline trajectories of adults of higher or lower than average
384 education^{159,199}. Some questionnaires have been proposed, such as the Cognitive Reserve Index
385 questionnaire, which take into account the multiple aspects of CR²⁰⁰; studies that have included social
386 engagement and occupational attainments as components of CR have reported consistent findings of its
387 beneficial impact on cognitive ageing²⁰¹⁻²⁰³.

388 The inconsistency in defining and measuring CR has made the investigation into its neurobiological
389 underpinnings particularly challenging¹⁹¹, but some findings have been replicated by different researchers
390 and on different cohorts of participants. Although high CR does not offset structural brain ageing, as
391 indexed by similar levels of objective brain lesions¹⁹⁴, protein burden^{197,198} or cortical atrophy²⁰⁴
392 irrespective of CR scores, those with high CR appear to be more resilient to this brain deterioration, so that
393 the same extent of objective substrate damage causes, comparatively, less cognitive impairment^{105,193};
394 functional imaging studies indicate that this is accompanied by more efficient patterns of metabolism in
395 posterior brain areas and increased activation and connectivity in the frontal lobes¹⁰⁵.

396 The interpretation of cognitive reserve as one's ability to sustain a higher degree of damage before
397 displaying overt symptoms closely resembles the definition of the metric of brain graph resilience^{205,206}.
398 Resilience is a concept derived from graph-theory which reflects a complex system's robustness to
399 progressive lesioning, i.e., the ability to compensate for the endured damage without losing its overall
400 characteristics and efficiency²⁰⁷. Although the precise genetic basis of CR and brain resilience have yet to be
401 clarified, studies suggest the heritability of both^{208,209}. Exploring the involvement of brain graph resilience as
402 a correlate of CR might provide interesting insights into its neurobiology.

403 **7. Deviating trajectories: cognitive performance in high CR individuals and AD patients**

404 The profile described in paragraphs 4a and 4b is typical of ordinary, cognitively healthy individuals.
405 However, trajectories can deviate both ways, displaying a better or worse than average performance. This
406 is the case for, respectively, individuals with high cognitive reserve (CR) and patients affected by dementia
407 (Figure 2b).

408 The most prevalent form of dementia is amnesic Alzheimer's disease (AD). Its cognitive symptoms are well
409 known and have been extensively described elsewhere²¹⁰ (Figure 2b, dotted line). Memory impairment is
410 typically the first reported symptom, although processing speed deficits seem to be the first to appear
411 objectively²¹¹, followed closely by executive and spatial deficits²¹⁰. Moreover, those crystallized functions
412 which are spared in typical healthy ageing also become impaired in AD patients: semantic knowledge²¹²,
413 autobiographical memory²¹³, automatic memory²¹⁴ and emotion regulation²¹⁰ all endure significant
414 deterioration with the progression of the disease.

415 On the contrary, individuals with high CR display particularly favourable outcomes (Figure 2b, solid line). A
416 recent longitudinal study conducted on 1697 individuals has assessed the influence of CR on cognitive
417 trajectories²⁰³. Measuring CR as a composite score including education, early, mid and late-life cognitive
418 activities and social engagement, the study showed that those with higher CR experience a longer cognitive
419 healthspan across all domains. Furthermore, having a high cognitive reserve protects from cognitive decline
420 even in patients with AD pathology, so much so that individuals with AD pathology but high CR scores and
421 individuals without AD pathology but low CR scores can display the exact same cognitive profile and decline
422 trajectories. This demonstrates the practical gains derived from considering the risk factors presented in
423 paragraph 3 and Table 1 and embracing the beneficial interventions proposed in the following paragraph.

424 **8. Beneficial active interventions to promote healthy brain ageing.**

425 Active interventions to promote healthy brain ageing can prolong the cognitive healthspan¹²⁷ (Figure 1,
426 bottom arrow). These target both cognitive and brain reserve and increase resilience to functional decline,
427 however, to the best of our knowledge, no study has systematically compared and quantified the impact of
428 concomitant risk and protective factors for cognitive decline. That is, how does the adoption of positive
429 habits, such as lifelong cognitive engagement, or the fortuitous lack of risk factors, like a history of TBI,
430 stack up with concomitant adverse conditions such as genetic predisposition, or risky behaviours such as
431 smoking? The pursuit of this line of research would be particularly interesting, considering most elderly
432 adult individuals present a mix of protective and risk factors in both their personal history and current
433 lifestyle.

434 Promising experimental interventions to prevent genetic degradation are in development. For instance,
435 new techniques are being studied with the aim of reversing age-related decline by promoting brain tissue
436 repair through epigenetic reprogramming^{215,216} and multiple clinical trials investigating the beneficial effect
437 of administering NAD⁺ precursors to increase NAD⁺ levels in healthy elderly adults are currently ongoing,
438 and hold encouraging results^{59,217,218}.

439 The brain's microstructure can be protected through several interventions. Among the best established of
440 these are sleep interventions²¹⁹. Disrupted sleep induces higher inflammation and decreased protein
441 clearance¹²⁷, which can be minimized by promoting slow waves during non-REM sleep²¹⁹. A randomized
442 control study (RCT) has indeed demonstrated that treating sleep disorders partially mitigates negative
443 effects on brain health²²⁰. Managing stress and depression also represents a viable intervention. In humans,
444 high stress levels are associated with increased oxidative stress and AD pathology, as well as decreased
445 brain volume and more prominent white matter lesions¹²⁷. RCTs demonstrate that stress reducing
446 practices, such as yoga or meditation, lead to improved cognitive functioning in ageing^{221,222}. On the other
447 hand, the importance of treating depression as a beneficial preventative intervention is debatable: it is hard
448 to disentangle the relationship between dementia and depression, because depression is considered both a
449 risk factor for and an early symptom of dementia. However, the correlation between depression and
450 cognitive decline is among the best-supported ones by empirical data²⁰ and, because of the relevant impact
451 depression has on stress and brain health and particularly on medial-temporal cortex integrity²²³, treating
452 depression is likely to benefit processes of brain ageing¹²⁷.

453 Among the most robust effective interventions are physical exercise and adopting a healthy diet²⁰. Exercise
454 yields an increase in BDNF concentration²²⁴ and insulin-like growth factor 1, promoting a healthier
455 metabolism²²⁵⁻²²⁷, and induces better sleep patterns^{228,229} in all age groups²²⁷. Moreover, physical exercise
456 interventions decrease overall AD pathology and brain volume loss, while strengthening the cardiovascular
457 system and thus decreasing the connected risks¹²⁷. A recent meta-analysis conducted on 15 international
458 cohorts has proven a direct negative association between regular daily exercise, computed as daily steps,
459 and all-cause mortality²³⁰; trials testing exercise interventions show it has cascading effects, improving
460 memory, mood, executive function and promoting brain plasticity^{127,231}. Interestingly, a recent study²³² that
461 examined 1369 adults found that pet ownership, by inducing beneficial behaviours such as walking
462 regularly and through its well-known positive effects on blood pressure and stress²³³, may be linked to
463 slower cognitive decline. The benefits of adopting a balanced and heart-healthy diet throughout the
464 lifespan, such as the Mediterranean diet²³⁴, are widely accepted²³⁵. Positively impacting cardiovascular
465 health, a heart-healthy diet protects from brain volume loss and is associated with lesser atrophy in the
466 hippocampal region and reduced AD pathology¹²⁷; also, some emerging studies have even linked the
467 Mediterranean diet with augmented telomere length²³⁶. RCTs have shown that these diets induce improved
468 global cognition and executive function²²⁵.

469 In the recent decades, several studies have focussed on behavioural interventions²²⁵ (i.e., physical activity,
470 social interventions, cognitive stimulation), and have obtained significant and encouraging findings. The
471 importance of the social environment should not be underestimated. Epidemiological evidence suggests
472 that less frequent social contact and feeling lonely are associated with increased dementia risk and
473 cognitive impairment²³⁷, although the relationship could to some extent be bidirectional. Interventions
474 aimed at promoting social engagement hold promising results, including increases in memory and
475 executive function^{238,239}, which is reflected in imaging studies as increased prefrontal and anterior cingulate
476 cortex activation²⁴⁰ and an overall higher brain volume²⁴¹.

477 The importance of remaining cognitively active throughout one's life is undisputed. However, measuring
478 the exact impact on brain health and cognitive function is somewhat challenging: the wide variety of
479 cognitive stimulation interventions are difficult to compare and loosely defined¹⁷⁷, ranging from daily
480 crosswords²⁴² to structured multisession programs¹⁸¹. However, converging evidence shows that late life
481 cognitive activity is associated with improved performance in memory, processing speed and executive
482 function, as well as reduced dementia risk^{149,180,181}. Critically, cognitive training programs and memory
483 training seem to be effective only if enacted before dementia onset²⁴³. The mechanisms underlying these
484 beneficial effects are still unclear¹²⁷. Potentially, it might be due to an increase in neuroplasticity, indexed
485 by a higher BDNF concentration recorded in older individuals after an intensive cognitive training

486 program²⁴⁴; other possible mechanisms include a reduction in AD pathology and maintained grey matter
487 volume¹²⁷.

488 Although more rigorous RCT on cognitive training are still needed to clearly define its efficacy¹⁷⁶, one RCT
489 conducted on a cohort of 1260 elderly participants, the Finnish Geriatric (FinGer) Intervention Study to
490 Prevent Cognitive Impairment and Disability, has found that the combination of multiple non-
491 pharmacological interventions (diet, exercise, cognitive training and vascular risk monitoring) may be
492 especially effective and beneficial²⁴⁵. This finding gave rise to the creation of a global network of ongoing
493 studies exploring the potential of multi-pronged approaches to reduce risk of cognitive impairment or
494 dementia²⁴⁶.

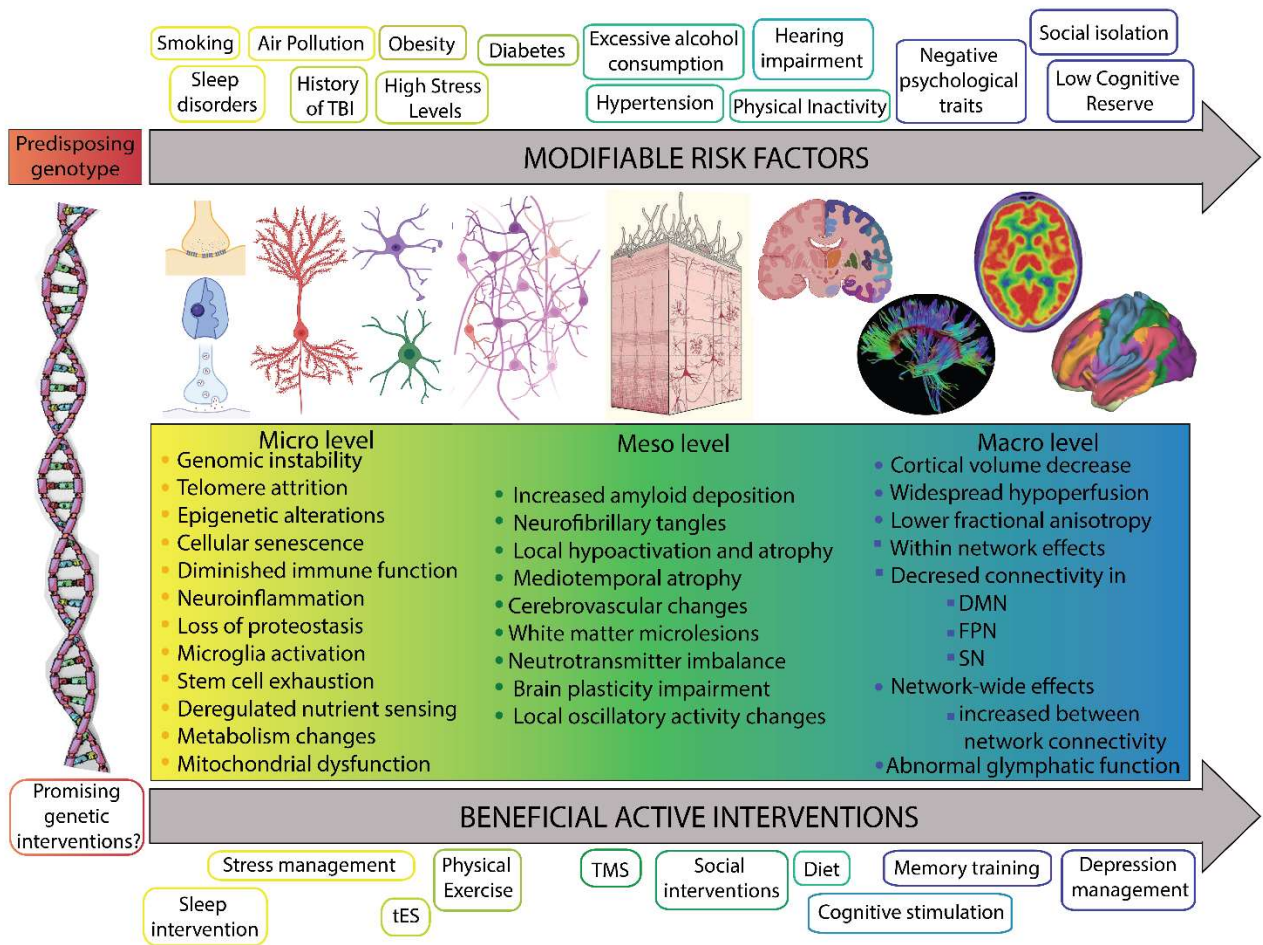
495 Finally, recent neuroscientific research has investigated the feasibility and efficacy of non-invasive brain
496 stimulation (NIBS) techniques to promote and preserve cognitive abilities in the healthy ageing brain²⁴⁷,
497 offering unique neuromodulation potential and minimal side effects. Transcranial magnetic stimulation
498 (TMS) can be applied using its multiple repetitive paradigms to increase synaptic efficiency and strength
499 (repetitive TMS, rTMS, and theta-burst stimulation, TBS)²⁴⁷ or to modulate cortical connectivity (cortico-
500 cortical paired associative stimulation, ccPAS)^{248,249}. Transcranial electric stimulation (tES) is based on the
501 application of electrical potentials with the aim of modulating intrinsic oscillatory brain activity (transcranial
502 alternating current stimulation, tACS) or to alter membrane polarisation and the spontaneous firing rate of
503 neurons (transcranial direct current stimulation, tDCS)²⁴⁷. Although both TMS and tES have been adopted to
504 modulate brain activity and cognition in the older individuals, TMS studies are strongly skewed toward
505 patient populations, and studied on the application of repetitive TMS protocols on healthy elderly
506 individuals are rarer²⁵⁰. Anodal tDCS to increase excitability of specific brain areas is the most frequently
507 adopted technique and evidence supports its effectiveness in improving episodic, semantic and working
508 memory, motor and cognitive control, and the feasibility of non-invasive brain stimulation treatments in
509 healthy older adults^{250,251}.

510 **9. Conclusions**

511 Cognitive functions and their neural underpinning physiologically decline with ageing following
512 characteristic trajectories, which can however be modified. In the present paper, we have summarized the
513 modifiable risk factors and the main beneficial interventions which could promote a healthy brain ageing
514 process and significantly cut the risk of cognitive decline in old age. Those who adhere to these
515 recommendations, indeed, do show a longer cognitive healthspan. The critical mediating factor which
516 moderates the relationship between structural and cognitive decline is Cognitive Reserve. A better
517 understanding of the neural substrate of Cognitive Reserve will provide further insight into relevant
518 markers of cognitive decline, allowing for the development of more precocious and prompt multi-pronged
519 interventions.

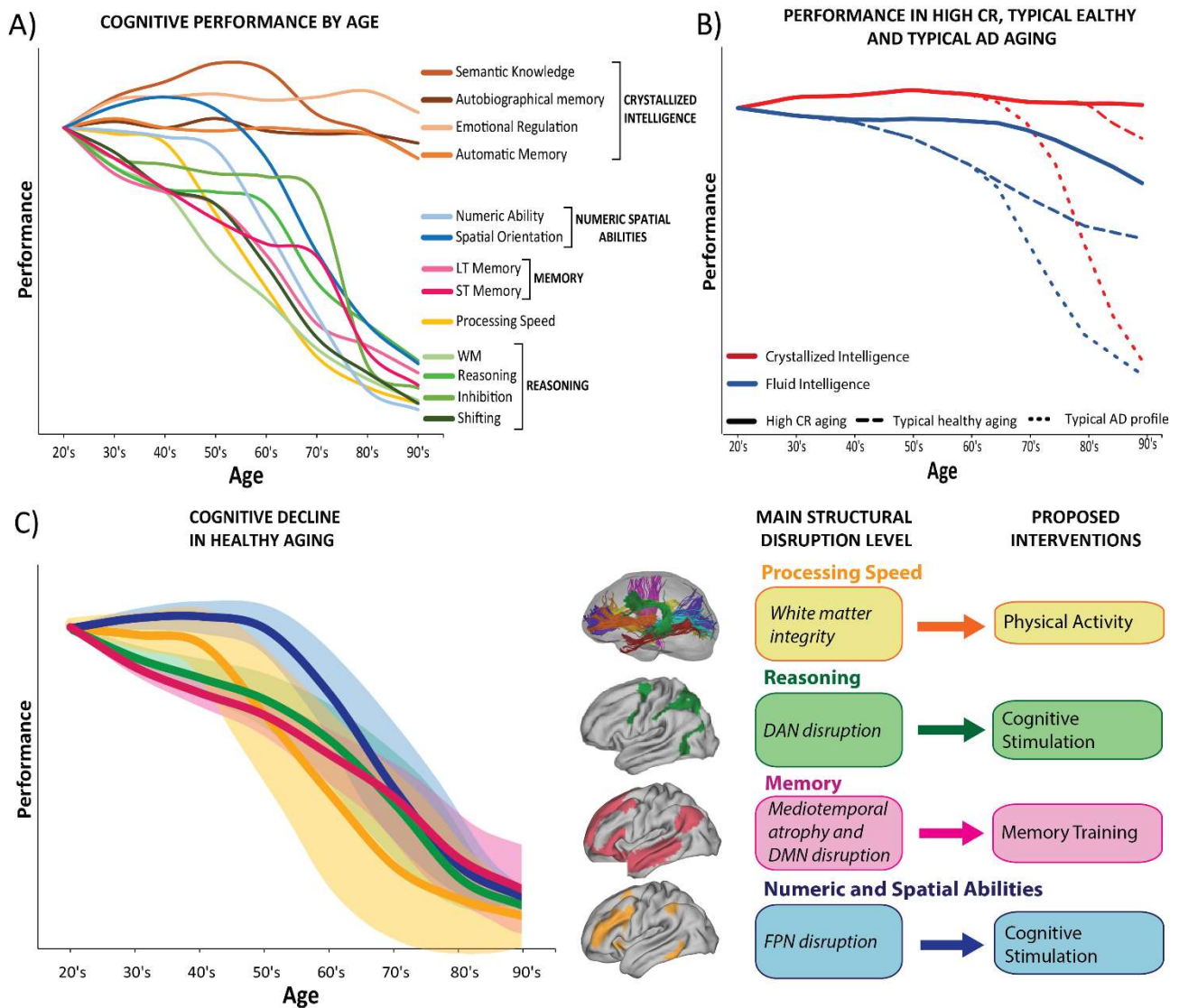
520

521 **Figure descriptions**



522

523 **Figure 1 – ageing from micro to macroscale.** Synopsis of changes the healthy brain endures through the lifespan, from
 524 the micro to the macroscopic level and the associated modifiable risk factors and beneficial active interventions to
 525 support a healthy ageing process.



526

527 **Figure 2 – The cognitive hallmarks of healthy ageing.** A) Trajectories displaying the typical performance across the
 528 lifespan of different cognitive functions. B) Different cognitive trajectories in crystallized (red) and fluid (blue) intelligence
 529 components in typical adults (dashed line), adults with high cognitive reserve (solid line) and adults with Alzheimer's
 530 Disease (dotted line). C) The age-related cognitive decline can be epitomized as a model comprising four main domains:
 531 Processing Speed, Reasoning, Memory and Numeric and Spatial Abilities.

532 **CRedit statement**

533 ST: conceptualization, Methodology, Visualization; Roles/Writing - original draft; Writing - review & editing;
 534 BW: Writing - review & editing, ME: Writing - review & editing, DP: Writing - review & editing, DAS: Writing -
 535 review & editing, GK: Writing - review & editing, AA: project administration, resources, supervision,
 536 Roles/Writing - original draft, Writing - review & editing; ES: conceptualization, project administration;
 537 resources; supervision; visualization, roles/Writing - original draft, writing - review & editing.

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540 **Declaration of interest**

541 Declarations of interest: none.

542

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