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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 pandemic<sup>1</sup>, this trend is projected to  
17       continue in the coming years in most industrialized countries<sup>2</sup>. 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 healthspan<sup>3</sup>, 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’<sup>4</sup>, 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”<sup>5</sup>. 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 Kahn<sup>6</sup>, 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 individuals<sup>7</sup>  
32       and, more recently, individuals displaying extraordinarily positive ageing outcomes (so called super-  
33       agers)<sup>8,9</sup>. The present review, instead, concentrates on usual healthy brain ageing<sup>7</sup>, 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 individuals<sup>10</sup> and propose potential beneficial active  
41       interventions to support cognitive reserve<sup>11</sup>, 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 macrostructural<sup>12</sup> 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 differences<sup>13</sup>; similar efforts have been made to estimate the heritability of  
53       healthy cognitive ageing<sup>14–18</sup>. 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)<sup>16</sup>. 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<sup>18–21</sup>. The

58 meta-analysis results indicate a polygenic model of inheritance<sup>16</sup>; 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, traits<sup>22</sup>. 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 lacking<sup>18</sup>.

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 it<sup>23</sup>, which represent widely investigated common denominators of the ageing  
70 process<sup>24</sup>: 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 primary<sup>23</sup> 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<sup>24,25</sup>. **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 damage<sup>23</sup>. Even  
78 under physiological conditions, the DNA is not chemically stable<sup>26</sup>; 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<sup>25,27</sup>. 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<sup>12,28</sup>. Although spontaneous DNA damage occurs randomly in all cell types on the order  
83 of tens of thousands of times per day<sup>26</sup>, some chromosomal regions are more prone to age-induced  
84 deterioration, such as telomeres, the terminal ends of DNA molecules<sup>29</sup>. Most mammalian cells do not  
85 express telomerase, the enzyme responsible for the replication of telomeres<sup>30</sup>; this results in **telomere**  
86 **attrition**, the physiological gradual and cumulative loss of chromosomes' ends protective caps during DNA  
87 replication<sup>29</sup>. 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<sup>24,31</sup>. Notably, promising genetic interventions are being studied in animal models, and indicate that  
90 premature ageing can be reverted in mice through telomerase reactivation<sup>32</sup>.

91 A further aspect of genomic instability are **epigenetic alterations**<sup>33</sup>. 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)<sup>12,24,34</sup>. Epigenetic mechanisms determine both the development and the  
96 deterioration of brain tissues (see here<sup>34</sup> for a review on epigenetics in neurodegeneration and  
97 neuroprotection) and are crucial for higher cognitive functions (e.g., memory)<sup>35</sup>. Multiple lines of evidence  
98 suggest that ageing is accompanied by epigenetic changes<sup>23</sup>; epigenetic clocks, thought to capture  
99 molecular ageing, are among the best-studied ageing biomarkers<sup>36,37</sup>.

100 DNA damage too extensive to be quickly repaired induces signalling events that can result in senescence,  
101 which plays a causal role in ageing<sup>25</sup>. **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 accumulation<sup>23</sup>. Because senescent cells secrete high levels of proinflammatory cytokines<sup>38</sup>, cellular  
106 senescence contributes to inflammation. Tissue inflammation is so typical of ageing that the term  
107 ‘inflammageing’ was coined<sup>39</sup>, and upregulated **neuroinflammation** studied as a marker of brain age<sup>24</sup>.  
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 efficacy<sup>12</sup>, the occurrence of improper autophagy<sup>40</sup>, and **loss of proteostasis** (i.e., the balance  
111 between protein synthesis, folding, trafficking, aggregation, disaggregation, and degradation)<sup>41</sup>. The  
112 proteostasis network becomes increasingly less efficient with age<sup>42</sup>, and the subsequent deposition of  
113 proteins is among the best-known correlates of normal ageing<sup>43</sup>. 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 disease<sup>44</sup>. Thus, proteomic clocks could  
116 be implemented and serve a similar purpose to epigenetic clocks<sup>36</sup>.

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 patterns<sup>45</sup>. 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 adults<sup>46</sup>, irrespective of their cognitive status<sup>47,48</sup>. Pathological **microglia activation** is believed  
123 to promote neurodegeneration<sup>46</sup> 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 clearance<sup>49</sup>.

126 To counteract tissue inflammation, the use of stem cells has been proposed<sup>50</sup>. The role of stem cells in  
127 healthy ageing<sup>51</sup> 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 brain<sup>52</sup>. 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**<sup>24,29,51</sup>.

132 Neuroinflammation is one of the most important **alterations in intercellular signalling** related to ageing. A  
133 second one is **deregulated nutrient sensing**<sup>23</sup>, which alters the metabolism and plays a critical role in the  
134 ageing process<sup>53</sup>. 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 ageing<sup>54</sup>. 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 ageing<sup>55</sup> and calorie restrictive diets, which downregulate nutrient signalling, have  
141 well-established neuroprotective effects<sup>56</sup>.

142 One further source of metabolism imbalance in ageing is **mitochondrial dysfunction**<sup>53</sup>. With advancing age,  
143 the efficacy of the respiratory chain dwindles, reducing ATP generation<sup>57</sup>; this phenomenon is particularly  
144 relevant in brain cells, as neurons are highly metabolically active<sup>58</sup>. 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 species<sup>24</sup>, adding to the oxidative damage of DNA and  
147 aggravating genomic instability. Among its consequences, persistent DNA damage depletes the coenzyme  
148 NAD<sup>+</sup><sup>59</sup>; indeed, an age-dependent reduction of NAD<sup>+</sup> has been demonstrated in healthy humans<sup>60</sup>. NAD<sup>+</sup> is  
149 an oxidation-reduction factor essential to energy metabolism and mitochondrial homeostasis<sup>59</sup> 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<sup>12,43</sup>. 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<sup>41,43</sup>. 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**<sup>61</sup> in older brains. Although manifesting on different timescales<sup>62</sup>, atrophy is observed across  
166 different multimodal associative brain regions, particularly the medial temporal and parietal cortex<sup>63</sup>.  
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**<sup>64</sup> and  
169 hypoactivation<sup>65</sup> have been especially extensively studied and reported.

170 The **cerebrovascular system** is impacted by age. Vessels tend to diminish in size<sup>12,66,67</sup>, capillaries to reduce  
171 in number<sup>68</sup> and microbleeds and small infarctions are common<sup>69</sup> 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 onwards<sup>70</sup>. Cerebrovascular causes have been indicated for the **white**  
174 **matter lesions** commonly observed in ageing<sup>12</sup>: an age-related loss of myelinated axons<sup>71</sup> and a decline in  
175 fractional anisotropy<sup>72</sup> 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<sup>68,73,74</sup>.

177 Intercellular communication impairment is one of the hallmarks of ageing discussed in the previous section  
178 with regards to inflammaging 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 serotonin<sup>63</sup>) with cascade effects on cognitive function;  
181 GABAergic and glutamate dysregulation<sup>75</sup> are of particular interest because of their implication in **brain**  
182 **plasticity**<sup>76</sup> 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 adults<sup>77</sup>; this is coupled with decreased activity in the gamma frequency band (30-80  
187 Hz)<sup>78</sup>. 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 inhibition<sup>79</sup>, 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 elderly<sup>80</sup>. Moreover, their impairment leads to aberrant  
191 modulation of intrinsic neuronal excitability and, subsequently, aberrant neuronal plasticity<sup>81</sup>. Indeed, local  
192 mechanisms of brain plasticity, and particularly synaptic plasticity<sup>82,83</sup>, are impaired in the ageing brain<sup>84,85</sup>.

## 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**<sup>86</sup>, 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 see<sup>87</sup>).

203 As discussed in the previous paragraph, cellular loss and **widespread hypoperfusion**<sup>70,88</sup> result in local  
204 atrophy<sup>61</sup> 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 matter<sup>89</sup>, accompanied by an increase in  
208 ventricular size and cerebrospinal fluid volume<sup>89</sup>. Cortical atrophy is particularly interesting because of its  
209 strong correlation with cognitive performance<sup>90</sup>.

210 Moreover, whole-brain structural and functional connectivity are similarly and coherently impacted by  
211 ageing<sup>91</sup>. Findings on structural metrics consistently describe **widespread decreases in fractional**  
212 **anisotropy** in older compared to younger adults<sup>72,91,92</sup> and age-related reduction in structural connectivity  
213 and efficiency starting from early adulthood<sup>93,94</sup>. 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 elderly<sup>95-98</sup>. 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)<sup>91,99</sup>.  
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<sup>91,100,101</sup>. 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 results<sup>102</sup>. 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 DMN<sup>103</sup> and reduced network-to-network segregation<sup>99</sup>, 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 contact<sup>104</sup>. 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 reserve<sup>105</sup>, 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 status<sup>106</sup>. For example, low income is associated with worse eating habits<sup>107</sup>, increased rate of school

240 dropout<sup>108</sup>, a higher probability of living in densely polluted areas<sup>109</sup> and diminished life expectancy<sup>110</sup>. 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-being<sup>111</sup>. In the United States, such factors are inextricably  
 243 linked to disparities in health care delivery and economic status in racial and ethnic minorities<sup>112,113</sup>.  
 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 low<sup>20</sup>. 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.

<b>Risk Factor</b>	<b>Level</b>	<b>Evidence</b>
<i>Air Pollution</i>	Micro	Animal models suggest airborne particulate pollutants accelerate neurodegenerative processes through cerebrovascular and cardiovascular disease, A $\beta$ deposition, and amyloid precursor protein processing <sup>104</sup> . A systematic review including 13 longitudinal studies found that exposure to air pollutants was associated with increased dementia risk <sup>114</sup> .
<i>Smoking</i>	Micro	Different systematic reviews confirm that active smoking increases the risk of dementia <sup>20,115</sup> . 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 <sup>104</sup> . Multiple studies and meta-analyses have confirmed that a history of TBI increases the risk of dementia <sup>116,117</sup> , even reporting a two-fold surge <sup>117</sup> . 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 <sup>118</sup> .
<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 <sup>119</sup> . Because of the critical role afforded to sleep in protein and neurotoxic waste clearance <sup>120</sup> , the primary proposed pathway revolves around diminished protein clearance function and subsequent pathological accumulation <sup>121</sup> .
<i>Obesity/weight</i>	Micro/Meso	Metabolic morbidity accelerates most of the hallmarks of brain ageing (e.g., neuroinflammation, impaired neuronal homeostasis) <sup>56</sup> . Moreover, studies have documented reduced grey matter volume <sup>122</sup> and white matter integrity <sup>123</sup> in multiple brain regions and reduced functional connectivity <sup>124</sup> 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 atrophy<sup>125</sup>. In humans, high stress levels were found to be associated with increased neural inflammation and diminished immune responses<sup>126</sup> as well as decreased brain volume and more prominent white matter lesions<sup>127</sup>.</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 ageing<sup>126</sup>.</p>
<i>Diabetes</i>	Micro/Meso	Diabetes leads to vascular pathology <sup>128</sup> and to reduced hippocampal neurogenesis and neuroplasticity <sup>129</sup> . 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 <sup>20</sup> .
<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 <sup>130</sup> .
<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 <sup>131</sup> and increased dementia risk. Moreover, alcohol consumption is linearly negatively associated with grey and white matter volume <sup>132</sup> , 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 <sup>127</sup> .
<i>Hypertension</i>	Meso/Macro	Midlife hypertension is associated with reduced brain volumes and increased white matter hyperintensity volume <sup>104</sup> .
<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 <sup>20,133</sup> . Proposed pathways include the direct effects of depression on stress hormones, neuronal growth factors and hippocampal atrophy <sup>134</sup> .
<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 <sup>127</sup> . 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 <sup>105,135,136</sup> . Additionally, higher cognitive activity levels, especially in early life and in middle age, correlate with decreased A $\beta$ deposition <sup>127</sup> .

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 trajectories<sup>137</sup> (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<sup>138-142</sup>. 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)<sup>143,144</sup>, 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<sup>144-146</sup> and, critically, that it is hard to build a  
273 statistical model to effectively control for retest effects<sup>147</sup>. 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 time<sup>137</sup>. 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<sup>148-150</sup>. Similarly, working memory performance also linearly declines, both in its  
282 visuospatial and in its verbal components<sup>151-153</sup>. 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<sup>148,152,154-156</sup> and short-term memory<sup>157,158</sup> 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-fifties<sup>148</sup>. Spatial orientation seems to  
287 slightly increase until age 30<sup>148</sup>, then plateaus and only declines after one's sixties<sup>154,159</sup>. A similar pattern  
288 has been reported for reasoning abilities, which undergo a significant decline after the age of 50<sup>148,151,154,160</sup>.  
289 Shifting (i.e. mental set shifting) and inhibition abilities (i.e. inhibition of prepotent responses)<sup>161</sup> also  
290 display a late-life decrease<sup>150,154</sup>: 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 level<sup>145</sup>.

295 Cognitive functions which remain stable in life have been termed "crystallized intelligence"<sup>149</sup>. Semantic  
296 knowledge is one of them, increasing until the mid-fifties and only slightly lowering after age 70<sup>148,154-157,159</sup>.  
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 intact<sup>162</sup>, and data suggests that the elderly attend to the emotional content of memories more than young  
300 adults do<sup>137,163</sup>. 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 preserved<sup>164</sup>, especially for  
302 events occurring in young adulthood (for a review see<sup>165</sup>). Automatic memory, measured as the magnitude  
303 of priming effects, seems to remain intact until late age as well<sup>156,166</sup>.

304 Declining and stable cognitive functions are broadly referred to as fluid and crystallized, respectively<sup>149</sup>, 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 loss<sup>167</sup>; however, this generalized decline has not been  
308 consistently confirmed<sup>168</sup>. 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<sup>169,170</sup>.

#### 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 <sup>171</sup> and cross-sectional data<sup>160</sup> 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 impairment<sup>172</sup>. 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<sup>145,148,151</sup>; 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 integrity<sup>173</sup>, interventions known to promote its health, such as physical activity<sup>174</sup>, 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 speed<sup>175</sup>.

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 underway<sup>176</sup>, promising results hint that mnemonic stimulation  
331 could be a tool for long time memory maintenance<sup>177</sup>.

332 The aforementioned studies that have investigated latent components of cognitive decline<sup>160,171</sup> 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 abilities<sup>178</sup>. Although they are two separate functions, **numeric and spatial abilities** rely on the  
336 same neural substrate, centred around the frontoparietal network<sup>179</sup>, which can be preserved and  
337 enhanced through cognitive training<sup>149,180,181</sup>.

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 inferences<sup>171</sup>. However, taking into  
341 consideration the overlapping neural substrates underlying these processes<sup>182</sup>, 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')<sup>161</sup>. 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<sup>183,184</sup>. Reasoning abilities, too,  
346 draw positive benefits from cognitive training<sup>149,180,181</sup>.

#### 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 undetected<sup>185</sup>.

353 Shifting from pen and paper cognitive assessment and stimulation tools to computerized methods, besides  
354 potentially yielding better results<sup>186</sup> 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 saccades<sup>187</sup>, biomarkers derived from human voice<sup>188</sup>,  
357 the use of wearables such as actigraphs to track sleep and other health parameters<sup>189</sup> and the recording of  
358 pen pressure or speed in drawing and writing tasks<sup>190</sup> 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 markers<sup>36</sup>. 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 function<sup>191</sup>. 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 studies<sup>192</sup>.

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<sup>193,194</sup>, 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<sup>11,105</sup>. 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 processing<sup>195</sup>.  
376 Although potentially influenced by common lifestyle factors, cognitive reserve and brain  
377 maintenance/reserve are two separate, uncorrelated processes<sup>196</sup>.

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<sup>193,197,198</sup>; 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<sup>159,199</sup>. Some questionnaires have been proposed, such as the Cognitive Reserve Index  
385 questionnaire, which take into account the multiple aspects of CR<sup>200</sup>; 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 ageing<sup>201-203</sup>.

388 The inconsistency in defining and measuring CR has made the investigation into its neurobiological  
389 underpinnings particularly challenging<sup>191</sup>, 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 lesions<sup>194</sup>, protein burden<sup>197,198</sup> or cortical atrophy<sup>204</sup>  
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<sup>105,193</sup>;  
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 lobes<sup>105</sup>.

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<sup>205,206</sup>.  
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 efficiency<sup>207</sup>. Although the precise genetic basis of CR and brain resilience have yet to be  
401 clarified, studies suggest the heritability of both<sup>208,209</sup>. 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 elsewhere<sup>210</sup> (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 objectively<sup>211</sup>, followed closely by executive and spatial deficits<sup>210</sup>. Moreover, those crystallized functions  
412 which are spared in typical healthy ageing also become impaired in AD patients: semantic knowledge<sup>212</sup>,  
413 autobiographical memory<sup>213</sup>, automatic memory<sup>214</sup> and emotion regulation<sup>210</sup> 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 trajectories<sup>203</sup>. 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 healthspan<sup>127</sup> (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<sup>215,216</sup> and multiple clinical trials investigating the beneficial effect  
437 of administering NAD<sup>+</sup> precursors to increase NAD<sup>+</sup> levels in healthy elderly adults are currently ongoing,  
438 and hold encouraging results<sup>59,217,218</sup>.

439 The brain's microstructure can be protected through several interventions. Among the best established of  
440 these are sleep interventions<sup>219</sup>. Disrupted sleep induces higher inflammation and decreased protein  
441 clearance<sup>127</sup>, which can be minimized by promoting slow waves during non-REM sleep<sup>219</sup>. A randomized  
442 control study (RCT) has indeed demonstrated that treating sleep disorders partially mitigates negative  
443 effects on brain health<sup>220</sup>. 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 lesions<sup>127</sup>. RCTs demonstrate that stress reducing  
446 practices, such as yoga or meditation, lead to improved cognitive functioning in ageing<sup>221,222</sup>. 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 data<sup>20</sup> and, because of the relevant impact  
451 depression has on stress and brain health and particularly on medial-temporal cortex integrity<sup>223</sup>, treating  
452 depression is likely to benefit processes of brain ageing<sup>127</sup>.

453 Among the most robust effective interventions are physical exercise and adopting a healthy diet<sup>20</sup>. Exercise  
454 yields an increase in BDNF concentration<sup>224</sup> and insulin-like growth factor 1, promoting a healthier  
455 metabolism<sup>225-227</sup>, and induces better sleep patterns<sup>228,229</sup> in all age groups<sup>227</sup>. Moreover, physical exercise  
456 interventions decrease overall AD pathology and brain volume loss, while strengthening the cardiovascular  
457 system and thus decreasing the connected risks<sup>127</sup>. 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 mortality<sup>230</sup>; trials testing exercise interventions show it has cascading effects, improving  
460 memory, mood, executive function and promoting brain plasticity<sup>127,231</sup>. Interestingly, a recent study<sup>232</sup> 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 stress<sup>233</sup>, 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 diet<sup>234</sup>, are widely accepted<sup>235</sup>. 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 pathology<sup>127</sup>; also, some emerging studies have even linked the  
467 Mediterranean diet with augmented telomere length<sup>236</sup>. RCTs have shown that these diets induce improved  
468 global cognition and executive function<sup>225</sup>.

469 In the recent decades, several studies have focussed on behavioural interventions<sup>225</sup> (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 impairment<sup>237</sup>, 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<sup>238,239</sup>, which is reflected in imaging studies as increased prefrontal and anterior cingulate  
476 cortex activation<sup>240</sup> and an overall higher brain volume<sup>241</sup>.

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 defined<sup>177</sup>, ranging from daily  
480 crosswords<sup>242</sup> to structured multisession programs<sup>181</sup>. 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<sup>149,180,181</sup>. Critically, cognitive training programs and memory  
483 training seem to be effective only if enacted before dementia onset<sup>243</sup>. The mechanisms underlying these  
484 beneficial effects are still unclear<sup>127</sup>. 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 program<sup>244</sup>; other possible mechanisms include a reduction in AD pathology and maintained grey matter  
487 volume<sup>127</sup>.

488 Although more rigorous RCT on cognitive training are still needed to clearly define its efficacy<sup>176</sup>, 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 beneficial<sup>245</sup>. 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 dementia<sup>246</sup>.

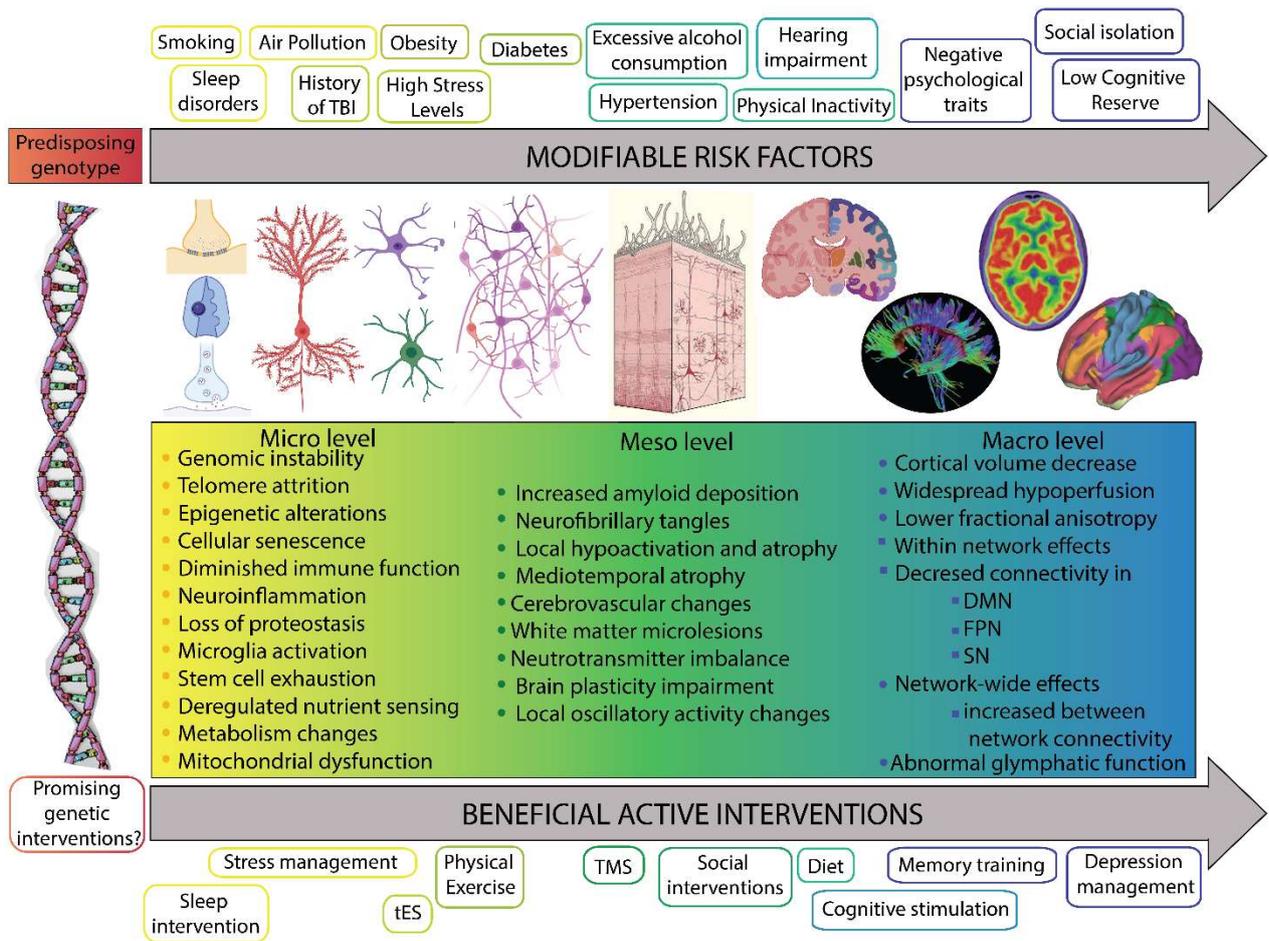
495 Finally, recent neuroscientific research has investigated the feasibility and efficacy of non-invasive brain  
496 stimulation (NIBS) techniques to promote and preserve cognitive abilities in the healthy ageing brain<sup>247</sup>,  
497 offering unique neuromodulation potential and minimal side 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)<sup>247</sup> or to modulate cortical connectivity (cortico-  
500 cortical paired associative stimulation, ccPAS)<sup>248,249</sup>. 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)<sup>247</sup>. 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 rarer<sup>250</sup>. 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<sup>250,251</sup>.

## 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.

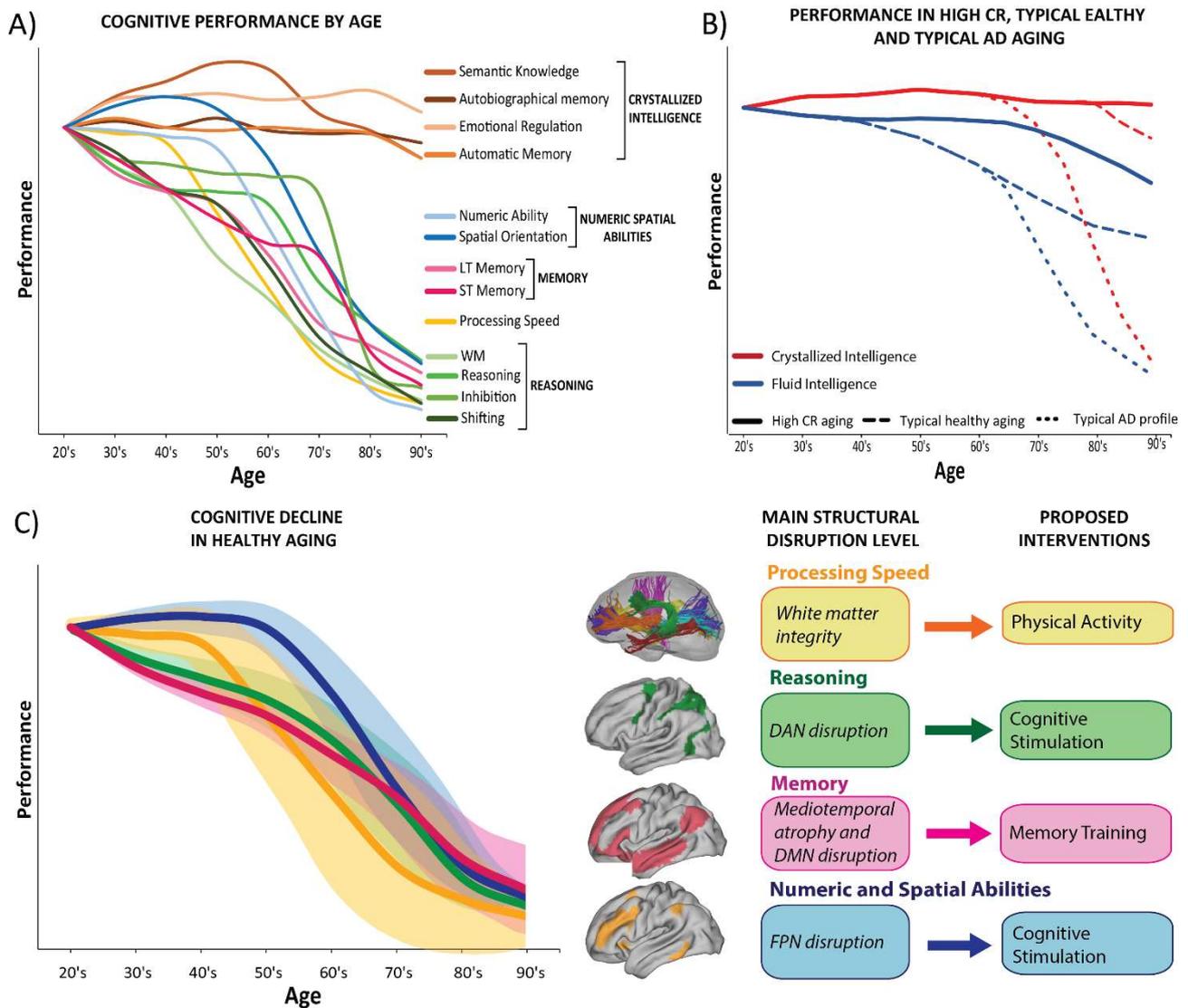
520

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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