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

Abstract

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

1. Introduction – Defining Healthy Brain Ageing

The past 250 years have seen a steady increase in the average human life expectancy and, although this trajectory has been temporarily altered by the recent Covid-19 pandemic[1], this trend is projected to continue in the coming years in most industrialized countries[2]. This notion is a compelling call to address the issue of promoting and supporting a healthy ageing process. Indeed, a lengthening lifespan does not necessarily align with an equally prolonged healthspan[3], defined as the average length of a healthy life. Postponing the onset and attenuating the severity of late-life morbidity, aptly defined as 'compression of morbidity'[4], has subsequently become a health priority.

The World Health Organisation (WHO) defines healthy ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age"[5]. Therefore, the WHO's definition emphasizes that a healthy ageing trajectory is a 'process', a goal achieved throughout the lifespan to ensure the best possible outcome for one's later years. The definition relies on the concept of 'functional ability', qualified as "having the capabilities that enable all people to be and do what they have reason to value". This notion epitomizes the influential model proposed 25 years ago by Rowe and Kahn[6], which lists three main components of successful ageing: maintenance of physical and cognitive function, minimised risk of disability and continued engagement with life.

Embracing this framework, a significant spotlight should be afforded to healthy brain ageing. Seminal studies tackling the topic of ageing have traditionally focussed on cognitively disabled older individuals[7] and, more recently, individuals displaying extraordinarily positive ageing outcomes (so called super-agers)[8,9]. The present review, instead, concentrates on usual healthy brain ageing[7], which we define as the composite pattern of modifications the human brain physiologically endures with advancing age, from the anatomical, functional and cognitive standpoint, when adequate typical functional ability and adaptability are retained.

The first portion of our descriptive review will provide a synopsis of the anatomical transformations observed in the brain with advanced age, while also summarizing current findings on modifiable risk factors. Subsequently, we will relate these neural substrate modifications with the associated typical cognitive decline profile displayed by older individuals[10] and propose potential beneficial active interventions to support cognitive reserve[11], a mitigating factor preventing pathologic decline discussed in Paragraph 6.

2. Structural changes associated with healthy brain ageing.

Ageing physiologically causes a whole host of anatomical and functional modifications in the brain, ranging from the intracellular to macrostructural[12] levels. For the scope of this narrative review, we will discuss these changes in terms of microscale (i.e., intracellular), mesoscale (i.e., intercellular or local circuitry) and macroscale (i.e., whole brain, large scale networks) changes (Figure 1). However, it is important to note that we are not implying that these three levels are separate, nor that they should be studied as such. Indeed, they are better understood as an interconnected and mutually influential continuum.

2a. Predisposing genotypes

Several studies have investigated the heritability of longevity, estimating that around 25% of the variation in lifespan is caused by genetic differences[13]; similar efforts have been made to estimate the heritability of healthy cognitive ageing[14–18]. A meta-analysis of genome-wide association studies of 31 cohorts, considering a total sample size of almost 54 thousand healthy individuals, found a significant relationship between general cognitive function and four genes known to be related to the development of Alzheimer's disease (TOMM40, APOE, ABCG1 and MEF2C)[16]. Among them, the APOE e4 genotype was found by later studies to predict steeper cognitive decline in older adults even when not affected by Alzheimer's [18–21]. The

meta-analysis results indicate a polygenic model of inheritance[16]; in recent years the calculation of polygenic scores (PGS) has become common in research aiming to investigate genetic predictors of disease, health or, more generally, traits [22]. PGSs are extracted from published genome-wide association studies that have tested the correlation of millions of single-nucleotide polymorphisms with specific phenotypes (e.g., disease, educational attainment…); scores can then be computed on any individual genotype to measure the genetic probability of specific traits or the liability to a specific disease. However, although PGSs were found to predict cognitive performance across several domains in old age, evidence of their effectiveness in predicting cognitive decline is still lacking[18].

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2b. The Micro scale

A prominent review published almost ten years ago narrowed down the complex biology of ageing by identifying nine hallmarks of it [23], which represent widely investigated common denominators of the ageing process[24]: genomic instability, telomere attrition, epigenetic alterations, cellular senescence, altered intercellular communication, loss of proteostasis, stem cell exhaustion, deregulated nutrient sensing and mitochondrial dysfunction. These hallmarks are integrated, co-occurring and mutually causing one another, and can be adopted as a roadmap to discuss the microscale level changes occurring in the ageing brain.

DNA damage is considered among the primary[23] hallmarks of ageing, initiating a signalling cascade that reverberates through cells, driving them into apoptosis or senescence to avoid the replication of damaged genetic information[24,25]. ***Genomic instability*** is the increased tendency of the DNA to mutate, in response to both exogenous and endogenous factors, and the subsequent accumulation of genetic damage[23]. Even under physiological conditions, the DNA is not chemically stable[26]; additionally, it is vulnerable to chemical attacks by agents such as reactive oxygen species, resulting in prominent oxidative stress and consequent high levels of DNA mutations recorded in advanced age[25,27]. Indeed, older brain tissue presents increased DNA deletions rates (the removal of at least one nucleotide in a gene during DNA copying) and reduced ability for DNA repair[12,28]. Although spontaneous DNA damage occurs randomly in all cell types on the order of tens of thousands of times per day[26], some chromosomal regions are more prone to age-induced deterioration, such as telomeres, the terminal ends of DNA molecules[29] . Most mammalian cells do not express telomerase, the enzyme responsible for the replication of telomeres[30]; this results in ***telomere attrition***, the physiological gradual and cumulative loss of chromosomes' ends protective caps during DNA replication[29]. Telomere attrition limits the overall number of times any cell can replicate, slowly leading to cell loss in all organs with advancing age; thus, telomere attrition has been studied as a biomarker of brain age[24,31]. Notably, promising genetic interventions are being studied in animal models, and indicate that premature ageing can be reverted in mice through telomerase reactivation[32].

A further aspect of genomic instability are ***epigenetic alterations***[33]***.*** Epigenetic mechanisms regulate gene expression by changing the chemical structure of the DNA without affecting its coding sequence; epigenetic alterations consist of either the addition/removal of methyl groups from DNA (DNA methylation) or of changes to the histones, proteins that bind to DNA molecules in chromosomes (PARylation and acetylation of DNA and histones) [12,24,34]. Epigenetic mechanisms determine both the development and the deterioration of brain tissues (see here[34] for a review on epigenetics in neurodegeneration and neuroprotection) and are crucial for higher cognitive functions (e.g., memory)[35]. Multiple lines of evidence suggest that ageing is accompanied by epigenetic changes[23]; epigenetic clocks, thought to capture molecular ageing, are among the best-studied ageing biomarkers[36,37].

DNA damage too extensive to be quickly repaired induces signalling events that can results in senescence, which plays a causal role in ageing[25]. ***Cellular senescence*** is a stable arrest of the cell cycle, an adaptive mechanism by which the organism prevents the proliferation of damaged genetic material. Due to the phenomenon of 'contagious ageing', senescent cells induce senescence in neighbouring ones. The increase

in senescent cells generation, coupled with their deficient clearance results in their deleterious accumulation[23]. Because senescent cells secrete high levels of proinflammatory cytokines[38], cellular senescence contributes to inflammation. Tissue inflammation is so typical of ageing that the term 'inflammageing' was coined[39], and upregulated ***neuroinflammation*** studied as a marker of brain age[24]. Multiple other causes concur to the chronic inflammatory state observed in the ageing brain, such as invading pathogens, the accumulation of damaged tissue, neuronal injury, a decrease in the immune system efficacy[12], the occurrence of improper autophagy[40], and ***loss of proteostasis*** (i.e., the balance between protein synthesis, folding, trafficking, aggregation, disaggregation, and degradation) [41]. The proteostasis network becomes increasingly less efficient with age[42], and the subsequent deposition of proteins is among the best-known correlates of normal ageing[43]. A recent review of proteomic studies has identified over a thousand proteins that, across the whole human organism, including the brain, undergo modifications with age and are relevant to ageing and age-related disease [44]. Thus, proteomic clocks could be implemented and serve a similar purpose to epigenetic clocks[36].

Neuroinflammation is initiated by microglia, the immune cells in the central nervous system and primary source of proinflammatory cytokines. Under non-damaged conditions, microglia are physiologically in a homeostatic "resting" state; they become activated in response to exposure to pathogen-associated or damage-associated molecular patterns[45]. While microglia cells have a neuroprotective role in the young brain, multiple studies have shown that they gradually transition to a chronically activated and neurotoxic state in older adults[46], irrespective of their cognitive status[47,48]. Pathological ***microglia activation*** is believed to promote neurodegeneration[46] and an experimental intervention based on the induction of high frequency activity in the gamma frequency band has proven effective in modifying microglia, reducing inflammation and improving protein clearance[49].

To counteract tissue inflammation, the use of stem cells has been proposed[50]. The role of stem cells in healthy ageing[51] has been at the forefront of the scientific debate for a number of years, and exhaustively discussing it is beyond the scope of this review. Stem cells have been found in most tissues and organs in adult humans including, notably, the brain[52]. A stable populations of proliferating stem cells is necessary to the ability of tissues to recover from damage; however, with advanced age the number and proliferative capacity of stem cells decline, a phenomenon called ***stem cell exhaustion***[24,29,51].

Neuroinflammation is one of the most important ***alterations in intercellular signalling*** related to ageing. A second one is ***deregulated nutrient sensing*** [23]***,*** which alters the metabolism and plays a critical role in the ageing process[53]. Nutrient sensing is the ability of all cells, including neurons, to recognize nutrient levels within them and in the bloodstream and respond accordingly by absorbing, storing and converting nutrients to ensure energy provision and maintain blood nutrient levels within safe ranges (e.g., blood sugar levels). A wide range of nutrient signalling pathways, especially those involving insulin, are deregulated in ageing[54]. Excessive activation of nutrient-signalling pathways has been linked with negative ageing outcomes: genotypes that determine a lowered activity of nutrient-signalling pathways are also predictive of successful ageing[55] and calorie restrictive diets, which downregulate nutrient signalling, have well-established neuroprotective effects[56].

One further source of metabolism imbalance in ageing is ***mitochondrial dysfunction***[53]. With advancing age, the efficacy of the respiratory chain dwindles, reducing ATP generation[57]; this phenomenon is particularly relevant in brain cells, as neurons are highly metabolically active[58]. Although the link between mitochondrial dysfunction and ageing has not been fully elucidated yet, it is known that in the elderly brain damaged mitochondria overproduce reactive oxygen species[24], adding to the oxidative damage of DNA and aggravating genomic instability. Among its consequences, persistent DNA damage depletes the coenzyme NAD^{+}[59]; indeed, an age-dependent reduction of NAD^{+} has been demonstrated in healthy humans[60]. NAD^{+} is an oxidation-reduction factor essential to energy metabolism and mitochondrial homeostasis[59] so that its

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

2c. The Meso scale

Age-driven mesoscale modifications (i.e., impacting the intercellular or local circuitry level) are among the most studied phenomena concerning the ageing brain. The best known of them is the formation of ***neurofibrillary tangles*** (NFT) and ***amyloid plaques*** (AP), a firmly established characteristic of brains affected by dementia of the Alzheimer's type which is also observed in healthy ageing[12,43]. Neurofibrillary tangles form in the intracellular space; they are insoluble twisted fibres made mostly of tau protein, an essential building block of the microtubular structure that allows intracellular molecular transport. Amyloid plaques, instead, accumulate in the extracellular space; while protein fragments (i.e., amyloids) are broken down and removed in the healthy young brain, ageing causes protein clearance to decline, resulting in the accumulation of hard insoluble plaques of protein fragments between neurons[41,43]. One the one hand, the pathological misfolding of tau protein impacts the microtubule structures, which collapse and disrupt the intracellular trafficking of materials; on the other, plaques around nerve cells induce their death, conceivably by triggering an immune response. Thus, AP and NFT lead to ***local hypoactivation and atrophy***[61] in older brains. Although manifesting on different timescales[62], atrophy is observed across different multimodal associative brain regions, particularly the medial temporal and parietal cortex[63]. Because episodic memory loss is among the cognitive functions most susceptible to ageing, ***medial temporal (i.e., hippocampal, entorhinal and parahippocampal) grey matter atrophy*** [64] and hypoactivation[65] have been especially extensively studied and reported.

The ***cerebrovascular system*** is impacted by age. Vessels tend to diminish in size [12,66,67] , capillaries to reduce in number[68] and microbleeds and small infarctions are common[69] with advanced age, causing overall decreases in cerebral perfusion: blood flow to both the grey and white matter lowers by an estimated 0.5% every year from early adulthood onwards[70]. Cerebrovascular causes have been indicated for the ***white matter lesions*** commonly observed in ageing[12]: an age-related loss of myelinated axons[71] and a decline in fractional anisotropy[72] have been observed; the periventricular and deep subcortical white matter lesions in particular are thought to likely arise as a result of hypoperfusion and microvascular disease[68,73,74].

Intercellular communication impairment is one of the hallmarks of ageing discussed in the previous section with regards to inflammageing and deregulated nutrient sensing. At the larger neural population scale, intercellular communication is impaired by ***neurotransmitter imbalances***. Most neurotransmitters show decrements with age (e.g. dopamine and serotonine[63]) with cascade effects on cognitive function; GABAergic and glutamate dysregulation[75] are of particular interest because of their implication in ***brain plasticity***[76] and on ***local oscillatory activity changes.*** EEG and MEG studies found that healthy ageing is characterized by changes in several metrics of resting state oscillatory activity (frequency, power, morphology and distribution). Background oscillatory activity tends to slow down in the elderly, with the alpha rhythm (8-13 Hz) becoming dominant, and an increase in delta (0.1-4 Hz) and theta (4-8 Hz) power with respect to young adults[77]; this is coupled with decreased activity in the gamma frequency band (30-80 Hz)[78]. The decrease in oscillatory activity in the gamma band is particularly interesting; previous studies have tied local activation in the gamma frequency band to peri-somatic inhibition[79], which relies on the activation of Parvalbumin-positive intracortical inhibitory GABAergic nets whose dysfunction accounts for the reduction in gamma power observed in the elderly[80]. Moreover, their impairment leads to aberrant modulation of intrinsic neuronal excitability and, subsequently, aberrant neuronal plasticity[81]. Indeed, local mechanisms of brain plasticity, and particularly synaptic plasticity[82,83], are impaired in the ageing brain[84,85].

2d. The Macro scale

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

Recently, a brain-wide cerebrospinal fluid and interstitial fluid drainage pathway was characterized, the glymphatic system. The glial-lymphatic system of vessels channels extracellular fluid within the central nervous system to clear interstitial metabolic waste from the brain parenchyma; recent evidence suggests that ageing leads to an ***abnormal glymphatic function***[86], which results in the accumulation of metabolic waste in the extracellular space, such as amyloid fragments which, as discussed in paragraph 2c, contribute to neuronal death and cortical atrophy (for a review see[87]).

As discussed in the previous paragraph, cellular loss and ***widespread hypoperfusion***[70,88] result in local atrophy[61] across the entire brain; therefore, an overall ***decrease in cortical volume and thickness*** is observed in older individuals. A recent study, which pooled structural MRIs of more than 100,000 human participants, measured brain volumes during the lifespan and found that both grey and white matter volumes decline over time, with steeper declines for the grey matter[89], accompanied by an increase in ventricular size and cerebrospinal fluid volume[89]. Cortical atrophy is particularly interesting because of its strong correlation with cognitive performance[90].

Moreover, whole-brain structural and functional connectivity are similarly and coherently impacted by ageing[91]. Findings on structural metrics consistently describe ***widespread decreases in fractional anisotropy*** in older compared to younger adults[72,91,92] and age-related reduction in structural connectivity and efficiency starting from early adulthood[93,94]. Studies focussing on functional connectivity also report age-related modifications: first, the ageing brain is characterized by ***within network effects,*** i.e., alterations of synchronized activity between nodes of cortical networks. Key brain networks such as the default mode network (DMN), the frontoparietal network (FPN) and the salience network (SN) all show a ***decreased within network connectivity*** in the elderly[95–98]. Second, between-network effects have been found in normal ageing. These include ***increased between network-connectivity*** (i.e., increased positive correlations between networks that are not typically coupled and decreased anticorrelations between networks)[91,99]. This has been interpreted as a loss of functional system segregation between large-scale networks subserving cognition and it may potentially reflect an over-recruitment compensatory strategy[91,100,101]. It is worth noting that functional connectivity studies systematically measuring its changes during the lifespan are still scarce and not always consistent in their results[102]. Recent systematic reviews and meta-analyses have validated the findings described above, especially confirming the reported disruption of within network connectivity in the DMN[103] and reduced network-to-network segregation[99], but further second level evidence is still needed.

3. Modifiable risk factors

Based on the most recent report from the Lancet commission on dementia prevention, twelve modifiable risk factors have been identified which might delay or avoid dementia and promote healthy ageing: excessive alcohol consumption, history of traumatic brain injury (TBI), exposure to air pollution, lower education level, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes and infrequent social contact [104]. After reviewing the available literature, we propose two additional modifiable risk factors: high stress exposure and sleep fragmentation/sleep disorders (Figure 1, top arrow). In this revised framework, we included depression into the broader construct of negative psychological traits. Furthermore, we integrate low education level into the wider concept of cognitive reserve[105], which is also related to IQ, occupational attainment, physical fitness, and several other lifelong exposures discussed in paragraph 6.

Some authors propose that several risk factors for cognitive decline could be traced to low socioeconomic status[106]. For example, low income is associated with worse eating habits[107], increased rate of school

dropout[108], a higher probability of living in densely polluted areas[109] and diminished life expectancy[110]. A recent longitudinal study found that lower wealth predicts a steeper decline in physical, sensory and cognitive health, as well as in emotional well-being [111]. In the United States, such factors are inextricably linked to disparities in health care delivery and economic status in racial and ethnic minorities[112,113]. Therefore, when considering risk and protective factors to improve healthy ageing in the whole population, bridging disparities in social and racial inequalities must be considered.

The analysis of predisposing risk factors and beneficial interventions protecting from cognitive decline is for the most part based on observational studies; although the preferred research design, at least for interventions, would be a randomized clinical trial (RCT), it is often complex to build a study to be able to evaluate them in trials (e.g., educational attainment, lifelong physical fitness exercise). This can impact the quality of the available evidence on predisposing risk factors and beneficial interventions, which is sometimes low[20]. Because study designs are mainly limited to observational designs, improvements in research methods are needed, such as better validated standardized metrics of cognitive decline and exposure to risk/protective factors, as well as confirmatory second level evidence.

Risk Factor	**Level**	**Evidence**
Air Pollution	Micro	Animal models suggest airborne particulate pollutants accelerate neurodegenerative processes through cerebrovascular and cardiovascular disease, Aß 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].
Smoking	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.
History of TBI	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].
Sleep fragmentation/Sleep disorders	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].
Obesity/weight	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.
Chronic Stress	Micro / Meso	Chronic stress leads to the secretion of glucocorticoids, such as cortisol, whose excessive level is harmful to brain structures; research

		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[125]. In humans, high stress levels were found to be associated with increased neural inflammation and diminished immune responses[126] as well as decreased brain volume and more prominent white matter lesions[127]. 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[126].
Diabetes	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].
Hearing impairment	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].
Excessive Alcohol consumption	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.
Physical inactivity	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].
Hypertension	Meso/Macro	Midlife hypertension is associated with reduced brain volumes and increased white matter hyperintensity volume[104].
Negative Psychological Traits	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].
Social isolation	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).
Low Cognitive Reserve	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 Aβ deposition[127].

Table 1 - Modifiable risk factors impacting healthy brain ageing.

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4a. Cognitive hallmarks of healthy ageing

The physiological brain changes associated with age, described in paragraphs 2b, 2c and 2d, are accompanied by a typical decline in cognitive functions, which follow different trajectories[137] (Figure 2a). Note that the profile described here is a correlate of normal ageing, rather than a pathological outcome: it represents a natural decay in cognitive functions, similar to expected declines in physical functioning that accompany normal ageing. As such, the cognitive declines outlined here do not prohibit functional independence, particularly when compensatory strategies are engaged.

When reviewing the literature on the cognitive correlates of ageing, it is necessary to consider some methodological issues. Ageing cognitive trajectories can be studied adopting cross-sectional or longitudinal study designs, whose findings can sometimes be inconsistent. Inconsistencies can be ascribed, on the one hand, to cross-sectional study designs being flawed by well documented biases and inferential problems such as cohort effects, resulting in inappropriate estimations of the effect of age on cognition during the lifespan[138–142]. However, on the other hand, they could due to longitudinal study designs presenting retest or practice effects; positive gains due to retest have been reported even when time intervals are of considerable magnitude (above 5 years)[143,144], and could therefore be very complex to minimize in longitudinal study designs. Moreover, previous evidence indicates retest effects to have a rather large positive effect size, potentially masking age-related decline [144–146] and, critically, that it is hard to build a statistical model to effectively control for retest effects[147]. Based on these considerations on the impact of cohort and retest/practice effects, we included in the literature informing this section of the review on cognitive ageing both longitudinal and cross-sectional evidence with large sample sizes, and report findings with convergent support in both kinds of study designs.

Cognitive functions broadly follow three patterns of age-related change: some decline across the lifespan, some in late-life, and others are relatively stable, or even moderately increase over time[137]. Performance in life-long declining cognitive abilities decreases from its peak throughout the adult lifespan. The hallmark of cognitive ageing is decreased processing speed, which slowly declines in early adulthood and linearly recedes after age 40[148–150]. Similarly, working memory performance also linearly declines, both in its visuospatial and in its verbal components[151–153]. Critically, and in part due to the deterioration of working memory abilities, memory encoding abilities also decline from a very young age, resulting in worsened performance both in long term[148,152,154–156] and short-term memory[157,158] tasks.

Most cognitive functions, however, experience only slight declines until later in life. Numerical ability, measured through mathematical tests, is stable until one's mid-fifties[148]. Spatial orientation seems to slightly increase until age 30[148], then plateaus and only declines after one's sixties[154,159]. A similar pattern has been reported for reasoning abilities, which undergo a significant decline after the age of 50[148,151,154,160]. Shifting (i.e. mental set shifting) and inhibition abilities (i.e. inhibition of prepotent responses)[161] also display a late-life decrease[150,154]: performance steeply declines after 50 and 70 years of age, respectively. These late-life declining abilities are the ones most affected by discrepancies in results between longitudinal and cross-sectional measurements; indeed, although cross-sectional estimates demonstrate clear declines in spatial orientation and reasoning with ageing, longitudinal assessments support a maintenance of these functions at the individual level[145].

Cognitive functions which remain stable in life have been termed "crystallized intelligence"[149]. Semantic knowledge is one of them, increasing until the mid-fifties and only slightly lowering after age 70 [148,154–157,159]. Emotional regulation and processing seem to be maintained, or even improved, with age: for instance, performance in theory of mind tasks which require the attribution of mental states to others remains intact[162], and data suggests that the elderly attend to the emotional content of memories more than young adults do[137,163]. Although the most characteristic and recognisable symptom of old age is memory loss, not all memory functions decline with age. Autobiographical memory is largely preserved[164], especially for events occurring in young adulthood (for a review see[165]). Automatic memory, measured as the magnitude of priming effects, seems to remain intact until late age as well[156,166].

Declining and stable cognitive functions are broadly referred to as fluid and crystallized, respectively[149], and it has been put forth that fluid declines might be compensated for by retained crystallized abilities. According to the 'dedifferentiation hypothesis', however, all abilities deteriorate after the age of 85, potentially because of vision and hearing loss[167]; however, this generalized decline has not been consistently confirmed[168]. Moreover, recent studies have moved past this classical distinction and reported that, although they diverge in the steepness of their decline, rates of change correlate across all cognitive domains, so that individuals with greater losses in fluid abilities also display smaller gains, or even losses, in crystallized abilities[169,170].

4b. The four components of cognitive decline

The profile of physiological cognitive decline described in paragraph 4a can be characterized with a four-factor model (Figure 2C). Previous studies that have applied latent component analyses to both longitudinal [171] and cross-sectional data[160] report that, although the bulk of individual differences in cognitive decline can be attributed to domain general processes, a significant amount of it is accounted for by four distinct domains: processing speed, memory, reasoning and visuospatial function.

Processing speed, i.e. the ability to carry out mental operations quickly and efficiently, has been proposed as the prime indicator of cognitive ageing and the driving cause of other impairment [172]. Interestingly, however, some studies suggest that the impairment in other cognitive tests, especially memory and reasoning, emerges sooner in life than processing speed deficits[145,148,151]; yet, this could be accounted for by the fact that pure processing speed tests (e.g., letter or pattern comparison, finding A's) are very simple, and may be prone to ceiling effects. Because processing speed is known to heavily rely on general white matter integrity[173], interventions known to promote its health, such as physical activity[174], might be beneficial, as reported by a meta-analysis of randomized clinical trials on the effect of aerobic exercise training, which found it to be associated with improvements in processing speed[175].

Declarative memory, i.e. the ability to retrieve and state previously encoded information after a brief (short term memory) or long (long term memory) time interval, is notoriously linked to the activity and integrity of medial-temporal structures, which are essential nodes of the DMN. Although research on the definitive benefits of memory training is still underway[176], promising results hint that mnemonic stimulation could be a tool for long time memory maintenance[177].

The aforementioned studies that have investigated latent components of cognitive decline[160,171] include visuospatial function, i.e. the ability to mentally rotate 2D and 3D patterns, as one of their components. In the present review, we revisit this concept in light of novel findings that tightly link this capacity with numerical abilities[178]. Although they are two separate functions, ***numeric and spatial abilities*** rely on the same neural substrate, centred around the frontoparietal network [179], which can be preserved and enhanced through cognitive training[149,180,181].

Reasoning requires a complex and composite definition: it is the ability to divergently think, make use of unfamiliar information, identify relations, form concepts and draw inferences[171]. However, taking into consideration the overlapping neural substrates underlying these processes[182], we believe reasoning comprises the three "frontal lobe" executive functions: mental set shifting ('Shifting'), information updating and monitoring ('Working Memory'), and inhibition of prepotent responses ('Inhibition')[161]. This high-order reasoning factor has widespread neural bases, which mainly rely on the dorsal attention network, and to a lesser extent on both the left and right fronto-parietal control networks [183,184]. Reasoning abilities, too, draw positive benefits from cognitive training[149,180,181].

5. Entering the era of personalized brain health tracking

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

prospect of designing innovative tools to measure and track health daily, increasing the temporal resolution of traditional cognitive check-ups and giving access to an abundance of digital biometric measures so far undetected[185].

Shifting from pen and paper cognitive assessment and stimulation tools to computerized methods, besides potentially yielding better results[186] because of the increased interactive engagement, allows for the collection of more informative data. Eye-tracking technologies to assess dynamic vision and measure attention allocation through recording of fixation and saccades[187], biomarkers derived from human voice[188], the use of wearables such as actigraphs to track sleep and other health parameters[189] and the recording of pen pressure or speed in drawing and writing tasks[190] are all examples of viable metrics and potential proxies of general health and cognitive functioning; their application to tracking healthy brain ageing may become a key component of health monitoring .

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

Brain age may or may not align with chronological age, but it can be estimated by measuring structural and functional brain markers[36]. This roughly falls within the ambit of estimating one's brain reserve, defined as the 'neurobiological capital', or the quantifiable brain resources (e.g., synaptic count, intracranial volume, white and grey matter integrity) necessary to maintain adequate function[191]. The extent to which individual brains preserve their neurochemical, structural and functional integrity, at micro, meso and macro-scale levels, has also been referred to as "brain maintenance" in longitudinal studies[192].

The concept of brain maintenance implies that variations in structural characteristics would tightly correspond to a better cognitive performance. However, this is not always the case[193,194], as certain individuals display better coping abilities and mitigate the cognitive decline which would be expected based on their underlying brain damage. This raises the question of how to bridge the gap between one's brain structure, brain function and metrics of cognition. The construct of cognitive reserve (CR) was put forward as a moderator between brain pathology and its clinical outcome[11,105]. While brain reserve is a passive protective factor, based on the sheer amount of expendable substrate, CR is conceptualized as the brain's active coping in response to damage, through compensatory or pre-existing cognitive processing[195]. Although potentially influenced by common lifestyle factors, cognitive reserve and brain maintenance/reserve are two separate, uncorrelated processes[196].

One major hurdle to the research on CR is its measurement, which is to this day uneven across studies. The most frequently adopted proxy of CR is years of education[193,197,198]; however, high education alone is arguably a reductive index for this broader construct. Indeed, while it is true that individuals with higher education have higher scores in all cognitive domains, evidence casts doubt on the notion that high education per sé is a predictor of slower cognitive decay rates, as multiple studies on large sample sizes have reported no difference between the decline trajectories of adults of higher or lower than average education[159,199]. Some questionnaires have been proposed, such as the Cognitive Reserve Index questionnaire, which take into account the multiple aspects of CR [200]; studies that have included social engagement and occupational attainments as components of CR have reported consistent findings of its beneficial impact on cognitive ageing [201–203].

The inconsistency in defining and measuring CR has made the investigation into its neurobiological underpinnings particularly challenging[191], but some findings have been replicated by different researchers and on different cohorts of participants. Although high CR does not offset structural brain ageing, as indexed by similar levels of objective brain lesions [194], protein burden [197,198] or cortical atrophy [204] irrespective of CR scores, those with high CR appear to be more resilient to this brain deterioration, so that the same extent of objective substrate damage causes, comparatively, less cognitive impairment [105,193]; functional imaging studies indicate that this is accompanied by more efficient patterns of metabolism in posterior brain areas and increased activation and connectivity in the frontal lobes [105].

The interpretation of cognitive reserve as one's ability to sustain a higher degree of damage before displaying overt symptoms closely resembles the definition of the metric of brain graph resilience[205,206]. Resilience is a concept derived from graph-theory which reflects a complex system's robustness to progressive lesioning, i.e., the ability to compensate for the endured damage without losing its overall characteristics and efficiency[207]. Although the precise genetic basis of CR and brain resilience have yet to be clarified, studies suggest the heritability of both[208,209]. Exploring the involvement of brain graph resilience as a correlate of CR might provide interesting insights into its neurobiology.

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

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

The most prevalent form of dementia is amnesic Alzheimer's disease (AD). Its cognitive symptoms are well known and have been extensively described elsewhere[210] (Figure 2b, dotted line). Memory impairment is typically the first reported symptom, although processing speed deficits seem to be the first to appear objectively[211], followed closely by executive and spatial deficits[210]. Moreover, those crystallized functions which are spared in typical healthy ageing also become impaired in AD patients: semantic knowledge[212], autobiographical memory[213], automatic memory[214] and emotion regulation[210] all endure significant deterioration with the progression of the disease.

On the contrary, individuals with high CR display particularly favourable outcomes (Figure 2b, solid line). A recent longitudinal study conducted on 1697 individuals has assessed the influence of CR on cognitive trajectories[203]. Measuring CR as a composite score including education, early, mid and late-life cognitive activities and social engagement, the study showed that those with higher CR experience a longer cognitive healthspan across all domains. Furthermore, having a high cognitive reserve protects from cognitive decline even in patients with AD pathology, so much so that individuals with AD pathology but high CR scores and individuals without AD pathology but low CR scores can display the exact same cognitive profile and decline trajectories. This demonstrates the practical gains derived from considering the risk factors presented in paragraph 3 and Table 1 and embracing the beneficial interventions proposed in the following paragraph.

8. Beneficial active interventions to promote healthy brain ageing.

Active interventions to promote healthy brain ageing can prolong the cognitive healthspan[127] (Figure 1, bottom arrow). These target both cognitive and brain reserve and increase resilience to functional decline, however, to the best of our knowledge, no study has systematically compared and quantified the impact of concomitant risk and protective factors for cognitive decline. That is, how does the adoption of positive habits, such as lifelong cognitive engagement, or the fortuitous lack of risk factors, like a history of TBI, stack up with concomitant adverse conditions such as genetic predisposition, or risky behaviours such as smoking? The pursuit of this line of research would be particularly interesting, considering most elderly adult individuals present a mix of protective and risk factors in both their personal history and current lifestyle.

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

The brain's microstructure can be protected through several interventions. Among the best established of these are sleep interventions[219]. Disrupted sleep induces higher inflammation and decreased protein clearance[127], which can be minimized by promoting slow waves during non-REM sleep[219]. A randomized control study (RCT) has indeed demonstrated that treating sleep disorders partially mitigates negative effects on brain health[220]. Managing stress and depression also represents a viable intervention. In humans, high stress levels are associated with increased oxidative stress and AD pathology, as well as decreased brain volume and more prominent white matter lesions[127]. RCTs demonstrate that stress reducing practices, such as yoga or meditation, lead to improved cognitive functioning in ageing[221,222]. On the other hand, the importance of treating depression as a beneficial preventative intervention is debatable: it is hard to disentangle the relationship between dementia and depression, because depression is considered both a risk factor for and an early symptom of dementia. However, the correlation between depression and cognitive decline is among the best-supported ones by empirical data[20] and, because of the relevant impact depression has on stress and brain health and particularly on medial-temporal cortex integrity[223], treating depression is likely to benefit processes of brain ageing[127].

Among the most robust effective interventions are physical exercise and adopting a healthy diet[20]. Exercise yields an increase in BDNF concentration[224] and insulin-like growth factor 1, promoting a healthier metabolism[225–227], and induces better sleep patterns[228,229] in all age groups[227]. Moreover, physical exercise interventions decrease overall AD pathology and brain volume loss, while strengthening the cardiovascular system and thus decreasing the connected risks[127]. A recent meta-analysis conducted on 15 international cohorts has proven a direct negative association between regular daily exercise, computed as daily steps, and all-cause mortality[230]; trials testing exercise interventions show it has cascading effects, improving memory, mood, executive function and promoting brain plasticity[127,231]. Interestingly, a recent study[232] that examined 1369 adults found that pet ownership, by inducing beneficial behaviours such as walking regularly and through its well-known positive effects on blood pressure and stress[233], may be linked to slower cognitive decline. The benefits of adopting a balanced and heart-healthy diet throughout the lifespan, such as the Mediterranean diet[234], are widely accepted[235]. Positively impacting cardiovascular health, a heart-healthy diet protects from brain volume loss and is associated with lesser atrophy in the hippocampal region and reduced AD pathology[127]; also, some emerging studies have even linked the Mediterranean diet with augmented telomere length[236]. RCTs have shown that these diets induce improved global cognition and executive function[225].

In the recent decades, several studies have focussed on behavioural interventions[225] (i.e., physical activity, social interventions, cognitive stimulation), and have obtained significant and encouraging findings. The importance of the social environment should not be underestimated. Epidemiological evidence suggests that less frequent social contact and feeling lonely are associated with increased dementia risk and cognitive impairment[237], although the relationship could to some extent be bidirectional. Interventions aimed at promoting social engagement hold promising results, including increases in memory and executive function[238,239], which is reflected in imaging studies as increased prefrontal and anterior cingulate cortex activation[240] and an overall higher brain volume[241].

The importance of remaining cognitively active throughout one's life is undisputed. However, measuring the exact impact on brain health and cognitive function is somewhat challenging: the wide variety of cognitive stimulation interventions are difficult to compare and loosely defined[177], ranging from daily crosswords[242] to structured multisession programs[181]. However, converging evidence shows that late life cognitive activity is associated with improved performance in memory, processing speed and executive function, as well as reduced dementia risk[149,180,181]. Critically, cognitive training programs and memory training seem to be effective only if enacted before dementia onset[243]. The mechanisms underlying these beneficial effects are still unclear[127]. Potentially, it might be due to an increase in neuroplasticity, indexed by a higher BDNF concentration recorded in older individuals after an intensive cognitive training

program[244]; other possible mechanisms include a reduction in AD pathology and maintained grey matter volume[127].

Although more rigorous RCTon cognitive training are still needed to clearly define its efficacy[176], one RCT conducted on a cohort of 1260 elderly participants, the Finnish Geriatric (FinGer) Intervention Study to Prevent Cognitive Impairment and Disability, has found that the combination of multiple non-pharmacological interventions (diet, exercise, cognitive training and vascular risk monitoring) may be especially effective and beneficial[245]. This finding gave rise to the creation of a global network of ongoing studies exploring the potential of multi-pronged approaches to reduce risk of cognitive impairment or dementia[246].

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

9. Conclusions

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

Figure descriptions

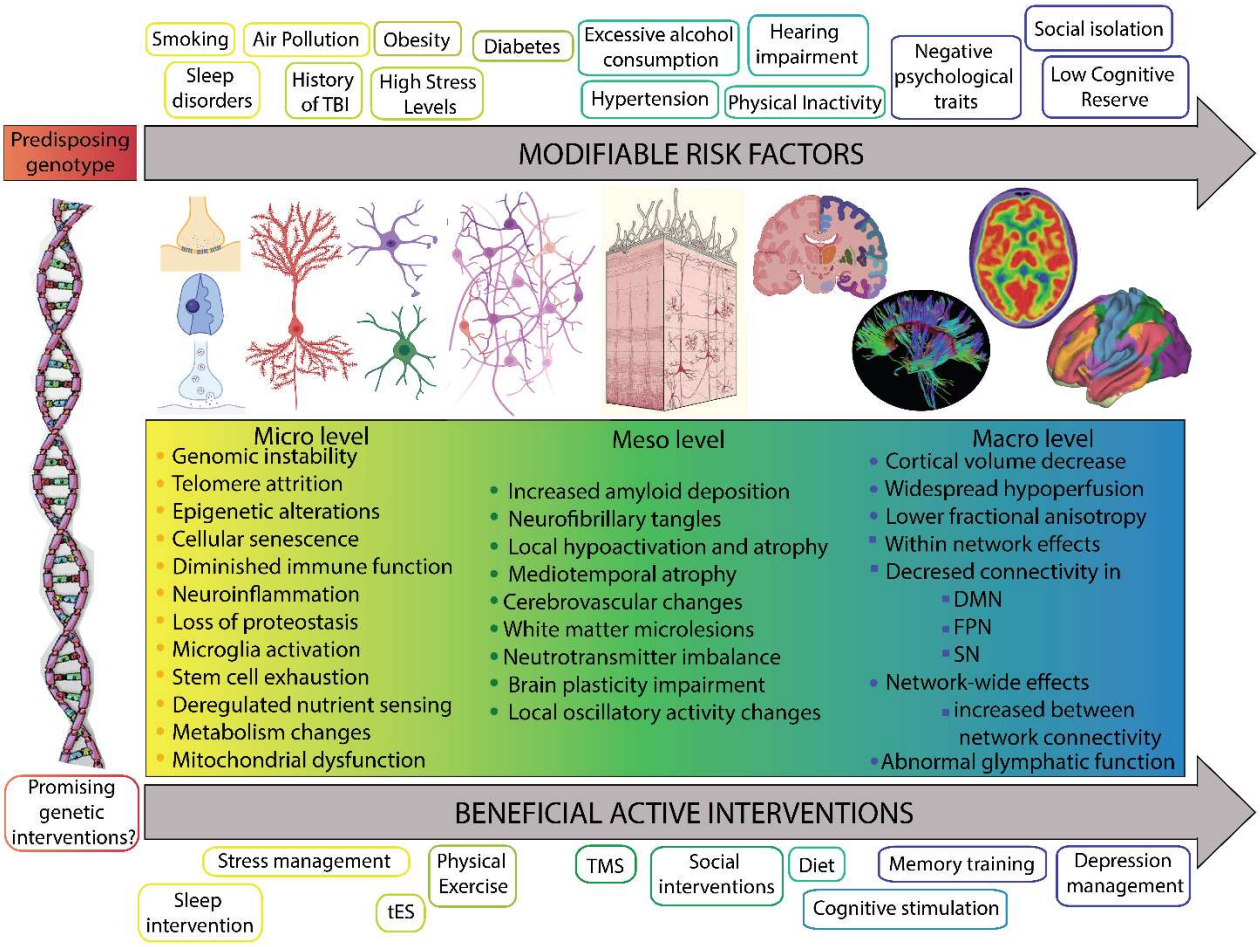

Figure 1 – ageing from micro to macroscale. *Synopsis of changes the healthy brain endures through the lifespan, from the micro to the macroscopic level and the associated modifiable risk factors and beneficial active interventions to support a healthy ageing process.*

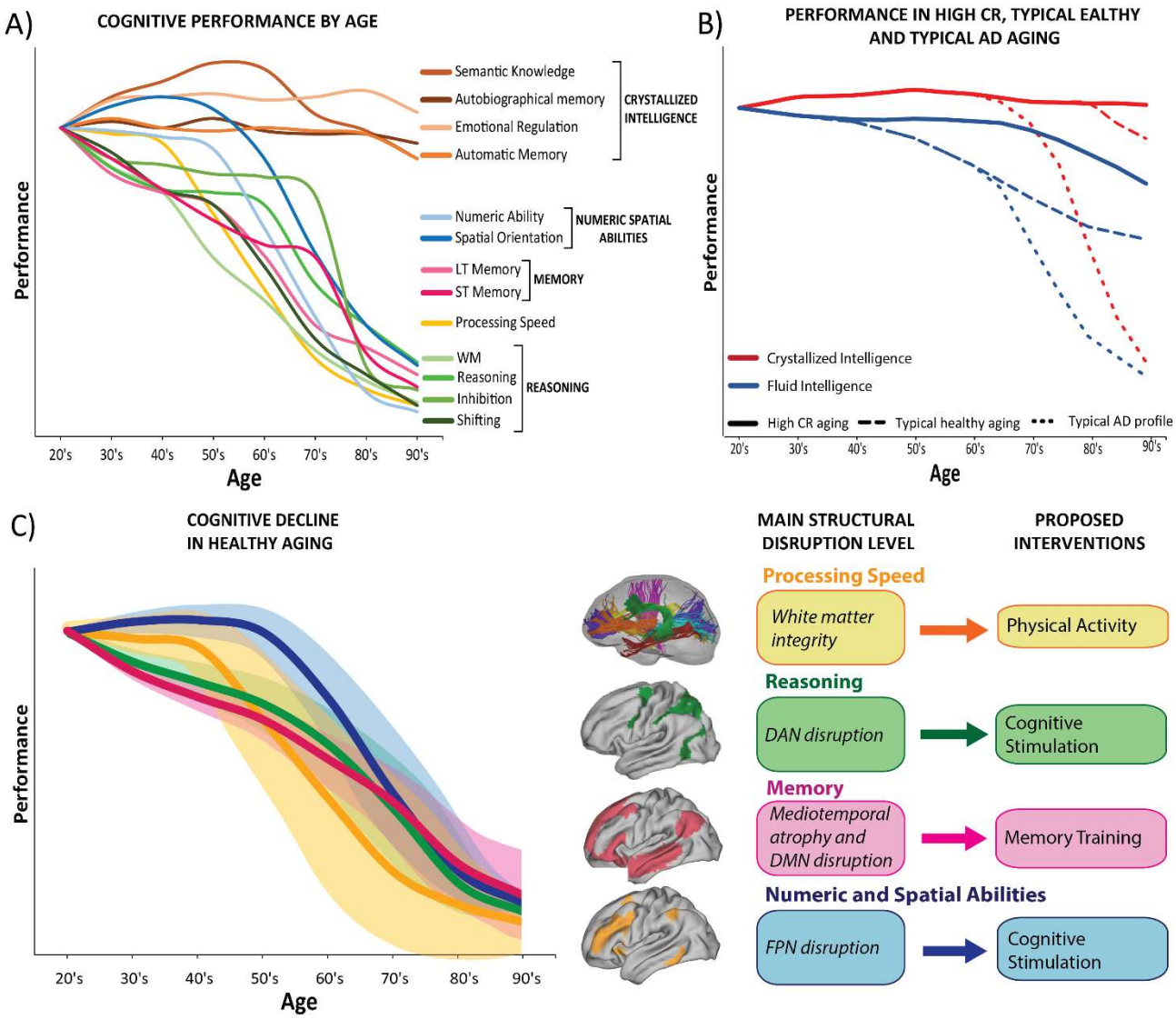

Figure 2 – The cognitive hallmarks of healthy ageing. *A) Trajectories displaying the typical performance across the lifespan of different cognitive functions. B) Different cognitive trajectories in crystallized (red) and fluid (blue) intelligence components in typical adults (dashed line), adults with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

CRediT statement

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

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Declaration of interest

Declarations of interest: none.

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