Ageing Research Reviews 88 (2023) 101939

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

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

Sonia Turrini [a,b], Bonnie Wong [c,d], Mark Eldaief [d,e], Daniel Z. Press [f], David A. Sinclair [g], Giacomo Koch [h,i], Alessio Avenanti [b,j], Emiliano Santarnecchi [a,*]

[a] Precision Neuroscience & Neuromodulation Program, Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[b] Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia "Renzo Canestrari", Alma Mater Studiorum Università di Bologna, Campus di Cesena, Cesena, Italy
[c] Neuropsychology Program, Frontotemporal Disorders Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA , USA
[d] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[e] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[f] Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[g] Blavatnik Institute, Department of Genetics, Paul F. Glenn Center for Biology of ageing Research, Harvard Medical School, Boston, MA, USA
[h] Stroke Unit, Department of Systems Medicine, University of Tor Vergata, Rome, Italy
[i] Department of Clinical and Behavioural Neurology, Santa Lucia Foundation IRCCS, Rome, Italy
[j] Centro de Investigación en Neuropsicología y Neurociencias Cognitivas, Universidad Católica del Maule, Talca, Chile

ARTICLE INFO

Keywords:
Healthy brain ageing
Cognitive reserve
Brain health
Cognitive ageing
Dementia

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 (Aburto et al., 2022), this trend is projected to continue in the coming years in most industrialized countries (Kontis et al., 2017). 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 (Crimmins, 2015), 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' (Partridge et al., 2018), 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" (WHO). 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 (Rowe and Kahn, 1997), 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

* Correspondence to: Associate Professor of Radiology, Harvard Medical School; Director, Precision Neuroscience & Neuromodulation Program Director, Department of Radiology, Massachusetts General Hospital Boston, MA, USA.
E-mail address: esantarnecchi@mgh.harvard.edu (E. Santarnecchi).

https://doi.org/10.1016/j.arr.2023.101939
Received 15 November 2022; Received in revised form 14 April 2023; Accepted 24 April 2023
Available online 27 April 2023

to healthy brain ageing. Seminal studies tackling the topic of ageing have traditionally focussed on cognitively disabled older individuals (Rowe and Kahn, 1987) and, more recently, individuals displaying extraordinarily positive ageing outcomes (so called super-agers) (De Godoy et al., 2021; Gefen et al., 2014). The present review, instead, concentrates on usual healthy brain ageing (Rowe and Kahn, 1987), 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 (Salthouse, 2014) and propose potential beneficial active interventions to support cognitive reserve (Stern, 2002), 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 (Cohen et al., 2019) 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 (Fig. 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.

2.1. Predisposing genotypes

Several studies have investigated the heritability of longevity, estimating that around 25% of the variation in lifespan is caused by genetic differences (Christensen et al., 2006); similar efforts have been made to estimate the heritability of healthy cognitive ageing (Davies, 2015; Gurland et al., 2004; Harris and Deary, 2011; Neuner et al., 2019; Ritchie et al., 2020). 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) (Davies, 2015). 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 (Handing et al., 2023; O'Donoghue et al., 2018; Plassman et al., 2010; Ritchie et al., 2020). The meta-analysis results indicate a polygenic model of inheritance (Davies, 2015); 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 (Lewis and Vassos, 2020). PGSs are extracted from

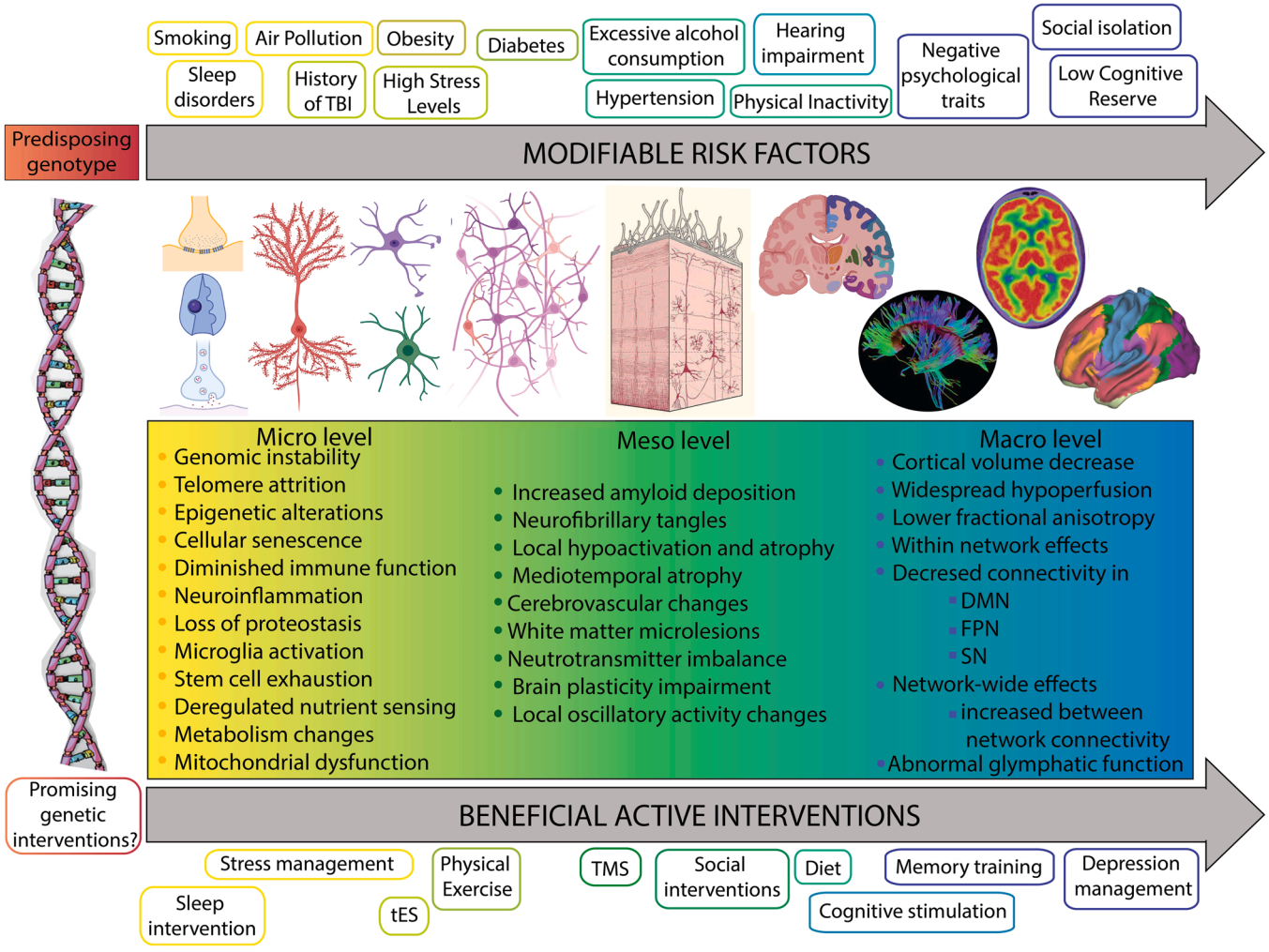

Fig. 1. Ageing from micro to macroscale. Synopsis of changes the healthy brain endures through the lifespan, from the micro to the macroscopic level and the associated modifiable risk factors and beneficial active interventions to support a healthy ageing process.

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 (Ritchie et al., 2020).

2.2. 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 (Hou et al., 2019): 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 (López-Otín et al., 2013) 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 (Hou et al., 2019; Yousefzadeh et al., 2021). ***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 (López-Otín et al., 2013). Even under physiological conditions, the DNA is not chemically stable (Lindahl, 1993); 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 (Salim, 2017; Yousefzadeh et al., 2021). 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 (Cohen et al., 2019; Maynard et al., 2015). Although spontaneous DNA damage occurs randomly in all cell types on the order of tens of thousands of times per day (Lindahl, 1993), some chromosomal regions are more prone to age-induced deterioration, such as telomeres, the terminal ends of DNA molecules (Blasco, 2007). Most mammalian cells do not express telomerase, the enzyme responsible for the replication of telomeres (Gorbunova and Seluanov, 2009); this results in ***telomere attrition***, the physiological gradual and cumulative loss of chromosomes' ends protective caps during DNA replication (Blasco, 2007). 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 (Bekaert and De Meyer, 2005; Hou et al., 2019). Notably, promising genetic interventions are being studied in animal models, and indicate that premature ageing can be reverted in mice through telomerase reactivation (Jaskelioff et al., 2011).

A further aspect of genomic instability are ***epigenetic alterations*** (Hayano et al., 2019). 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 (Hwang et al., 2017) for a review on epigenetics in neurodegeneration and neuroprotection) and are crucial for higher cognitive functions (e.g., memory) (Day and Sweatt, 2010). Multiple lines of evidence suggest that ageing is accompanied by epigenetic changes (López-Otín et al., 2013); epigenetic clocks, thought to capture molecular ageing, are among the best-studied ageing biomarkers (Higgins-Chen et al., 2021; McCartney et al., 2022).

DNA damage too extensive to be quickly repaired induces signalling events that can results in senescence, which plays a causal role in ageing (Yousefzadeh et al., 2021). ***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 (López-Otín et al., 2013). Because senescent cells secrete high levels of proinflammatory cytokines (Rodier and Campisi, 2011), cellular senescence contributes to inflammation. Tissue inflammation is so typical of ageing that the term 'inflammageing' was coined (Franceschi et al., 2000), and upregulated ***neuroinflammation*** studied as a marker of brain age (Hou et al., 2019). 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 (Cohen et al., 2019), the occurrence of improper autophagy (Salminen et al., 2012), 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 (Powers et al., 2009), and the subsequent deposition of proteins is among the best-known correlates of normal ageing (Fukumoto et al., 1996). 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 (Johnson et al., 2020). Thus, proteomic clocks could be implemented and serve a similar purpose to epigenetic clocks (Higgins-Chen et al., 2021).

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 (Edler et al., 2021). 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 (Luo et al., 2010), irrespective of their cognitive status (Gefen, 2019; Niraula et al., 2017). Pathological ***microglia activation*** is believed to promote neurodegeneration (Luo et al., 2010) 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 (Iaccarino et al., 2016).

To counteract tissue inflammation, the use of stem cells has been proposed (Ennis et al., 2013). The role of stem cells in healthy ageing (Goodell and Rando, 2015) 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 (Obernier and Alvarez-Buylla, 2019). 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*** (Blasco, 2007; Goodell and Rando, 2015; Hou et al., 2019).

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 (Tidwell et al., 2017). 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 (Akintola and van Heemst, 2015). 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 (Fontana et al., 2010) and calorie restrictive diets, which downregulate nutrient signalling, have well-established neuroprotective effects (Mattson and Arumugam, 2018).

One further source of metabolism imbalance in ageing is ***mitochondrial dysfunction*** (Tidwell et al., 2017). With advancing age, the efficacy of the respiratory chain dwindles, reducing ATP generation (Green et al., 2011); this phenomenon is particularly relevant in brain cells, as neurons are highly metabolically active (Elia, 1992). 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 (Hou et al., 2019), adding to the oxidative damage of DNA and aggravating genomic instability. Among its consequences, persistent DNA damage depletes the coenzyme NAD^+ (Lautrup et al., 2019); indeed, an age-dependent reduction of NAD^+ has been demonstrated in healthy humans (Zhu et al., 2015). NAD^+ is an oxidation-reduction factor essential to energy metabolism and mitochondrial homeostasis (Lautrup et al., 2019) so that its depletion further aggravates mitochondrial dysfunction, in a detrimental loop that contributes to the ageing process.

2.3. 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 (Cohen et al., 2019; Fukumoto et al., 1996). 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 (Currais et al., 2017; Fukumoto et al., 1996). 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*** (Treusch et al., 2011) in older brains. Although manifesting on different timescales (Scahill et al., 2003), atrophy is observed across different multimodal associative brain regions, particularly the medial temporal and parietal cortex (Peters, 2006). Because episodic memory loss is among the cognitive functions most susceptible to ageing, ***medial temporal (i.e., hippocampal, entorhinal and parahippocampal) grey matter atrophy*** (Jack et al., 1998) and hypoactivation (Gutchess et al., 2005) have been especially extensively studied and reported.

The ***cerebrovascular system*** is impacted by age. Vessels tend to diminish in size [12,](Bullitt et al., 2010; Pantoni, 2010), capillaries to reduce in number (Brown et al., 2007) and microbleeds and small infarctions are common (Smith et al., 2015) 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 (Leenders et al., 1990). Cerebrovascular causes have been indicated for the ***white matter lesions*** commonly observed in ageing (Cohen et al., 2019): an age-related loss of myelinated axons (Marner et al., 2003) and a decline in fractional anisotropy (Sullivan and Pfefferbaum, 2006) 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 (Brown et al., 2007; Buckner, 2004; Fernando et al., 2006).

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 (Peters, 2006)) with cascade effects on cognitive function; GABAergic and glutamate dysregulation (Hermans et al., 2018) are of particular interest because of their implication in ***brain plasticity*** (Zacharopoulos et al., 2021) 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 (Ishii et al., 2017); this is coupled with decreased activity in the gamma frequency band (30–80 Hz) (Murty et al., 2020). 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 (Buzsáki and Wang, 2012), 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 (Cardin, 2009). Moreover, their impairment leads to aberrant modulation of intrinsic neuronal excitability and, subsequently, aberrant neuronal plasticity (Debanne et al., 2019). Indeed, local mechanisms of brain plasticity, and particularly synaptic plasticity (Lynch, 1998; Barnes, 2003), are impaired in the ageing brain (Arcos-burgos et al., 2019; Mahncke et al., 2006).

2.4. 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*** (Benveniste, 2019), 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 (Carlstrom et al., 2022)).

As discussed in the previous paragraph, cellular loss and ***widespread hypoperfusion*** (Leenders et al., 1990; Tarumi and Zhang, 2018) result in local atrophy (Treusch et al., 2011) 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 (Bethlehem et al., 2022), accompanied by an increase in ventricular size and cerebrospinal fluid volume (Bethlehem et al., 2022). Cortical atrophy is particularly interesting because of its strong correlation with cognitive performance (Lövdén et al., 2013).

Moreover, whole-brain structural and functional connectivity are similarly and coherently impacted by ageing (Damoiseaux, 2017). Findings on structural metrics consistently describe ***widespread decreases in fractional anisotropy*** in older compared to younger adults (Damoiseaux, 2017; Damoiseaux et al., 2009; Sullivan and Pfefferbaum, 2006) and age-related reduction in structural connectivity and efficiency starting from early adulthood (Gong, 2009; Zhao et al., 2015). 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 (Vidal-Piñeiro et al., 2014; Ng et al., 2016; Campbell et al., 2012; Touroutoglou et al., 2018). 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) (Damoiseaux, 2017; Deery et al., 2023). 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 (Damoiseaux, 2017; Ferreira, 2016; Spreng et al., 2016). 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 (Heckner et al., 2021). Recent systematic reviews and meta-analyses have validated the findings described above, especially confirming the reported disruption of within network connectivity in the DMN (Cansino, 2022) and reduced network-to-network segregation (Deery et al., 2023), 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 (Fig. 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 (Menardi et al., 2018), 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 (House et al., 1994). For example, low income is associated with worse eating habits (Alkerwi et al., 2015), increased rate of school dropout (Kearney and Levine, 2014), a higher probability of living in densely polluted areas (Mohai et al., 2009) and diminished life expectancy (Chetty et al., 2016). 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 (Steptoe and Zaninotto, 2020). In the United States, such factors are inextricably linked to disparities in health care delivery and economic status in racial and ethnic minorities (Noël, 2018; Ferraro et al., 2017). 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 (Plassman et al., 2010). 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.

3.1. 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 (Hedden and Gabrieli, 2004) (Fig. 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 (Baltes, 1980; Hofer and Sliwinski, 2006; Schaie, 2008; Kuhlen, 1961). 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) (Rabbitt et al., 2009; Salthouse et al., 2004), 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 (McArdle et al., 2002; Salthouse, 2009; Salthouse et al., 2004) and, critically, that it is hard to build a statistical model to effectively control for retest effects (Hoffman et al., 2011). 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 (Hedden and Gabrieli, 2004). 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 (Schaie et al., 2004; Park and Bischof, 2013; Salthouse, 2011). Similarly, working memory performance also linearly declines, both in its visuospatial and in its verbal components (Park et al., 2002; Park and Reuter-Lorenz, 2009; Salthouse and Davis, 2006). 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 (Nilsson et al., 1997; Nyberg et al., 1996; Park and Reuter-Lorenz, 2009; Salthouse, 2010; Schaie et al., 2004) and short-term memory (Christensen, 2001; Smith et al., 2002) 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 (Schaie et al., 2004). Spatial orientation seems to slightly increase until age 30 (Schaie et al., 2004), then plateaus and only declines after one's sixties (Salthouse, 2010; Berggren et al., 2018). A similar pattern has been reported for reasoning abilities, which undergo a significant decline after the age of 50 (Schaie et al., 2004; Salthouse and Davis, 2006; Salthouse, 2010; Salthouse and Ferrer-Caja, 2003). Shifting (i.e. mental set shifting) and inhibition abilities (i.e. inhibition of prepotent responses) (Miyake et al., 2000) also display a late-life decrease (Salthouse, 2011; Salthouse, 2010): 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

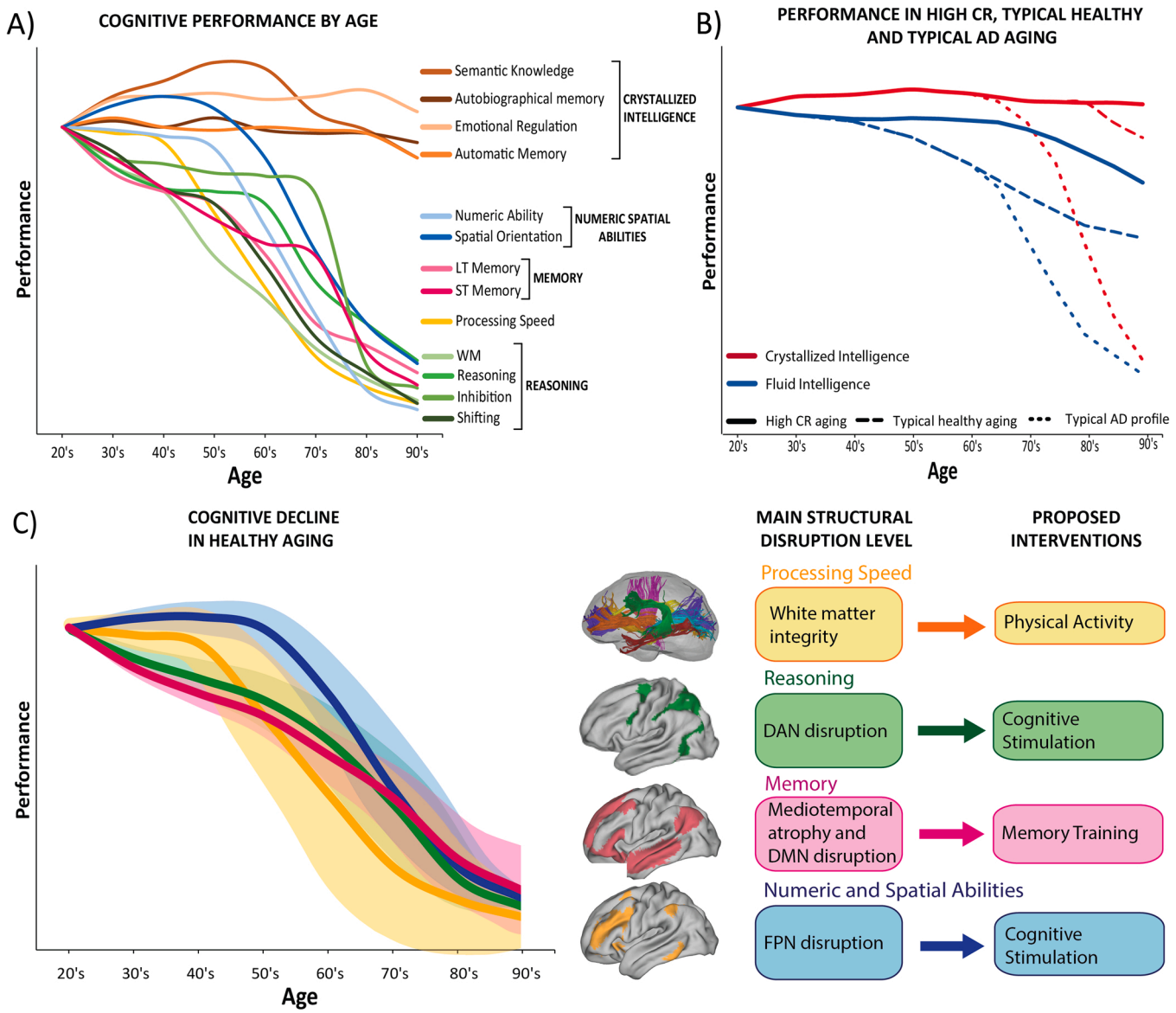

Fig. 2. . The cognitive hallmarks of healthy ageing. A) Trajectories displaying the typical performance across the lifespan of different cognitive functions. B) Different cognitive trajectories in crystallized (red) and fluid (blue) intelligence components in typical adults (dashed line), adults with 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.

assessments support a maintenance of these functions at the individual level (Salthouse, 2009).

Cognitive functions which remain stable in life have been termed "crystallized intelligence" (Park and Bischof, 2013). Semantic knowledge is one of them, increasing until the mid-fifties and only slightly lowering after age 70 (Berggren et al., 2018; Nilsson et al., 1997; Nyberg et al., 1996; Salthouse, 2010; Schaie et al., 2004; Smith et al., 2002). 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 (Happé et al., 1998), and data suggests that the elderly attend to the emotional content of memories more than young adults do (Hedden and Gabrieli, 2004; Carstensen et al., 2003). 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 (Fromholt et al., 2003), especially for events occurring in young adulthood (for a review see (Rubin, 2000)). Automatic memory, measured as the magnitude of priming effects, seems to remain intact until late age as well (La Voie and Light, 1994; Nilsson et al., 1997).

Declining and stable cognitive functions are broadly referred to as fluid and crystallized, respectively (Park and Bischof, 2013), 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 (Sánchez-Izquierdo and Fernández-Ballesteros, 2021); however, this generalized decline has not been consistently confirmed (Tucker-Drob and Salthouse, 2008). 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 (Tucker-Drob et al., 2019, 2022).

3.2. *The four components of cognitive decline*

The profile of physiological cognitive decline described in paragraph

4a can be characterized with a four-factor model (Fig. 2C). Previous studies that have applied latent component analyses to both longitudinal [171] and cross-sectional data (Salthouse and Ferrer-Caja, 2003) 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 (Salthouse, 1996). Interestingly, however, some studies suggest that the impairment in other cognitive tests, especially memory and reasoning, emerges sooner in life than processing speed deficits (Salthouse, 2009; Schaie et al., 2004; Salthouse and Davis, 2006); 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 (Penke et al., 2010), interventions known to promote its health, such as physical activity (Gow et al., 2012), 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 (Smith et al., 2010).

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 (Zehnder et al., 2009), promising results hint that mnemonic stimulation could be a tool for long time memory maintenance (Gates et al., 2011).

The aforementioned studies that have investigated latent components of cognitive decline (Salthouse and Ferrer-Caja, 2003; Tucker-Drob, 2011) 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 (Thompson et al., 2013). Although they are two separate functions, ***numeric and spatial abilities*** rely on the same neural substrate, centred around the frontoparietal network (Hawes et al., 2019), which can be preserved and enhanced through cognitive training (Park and Bischof, 2013; Yates et al., 2016; Ball et al., 2002).

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 (Tucker-Drob, 2011). However, taking into consideration the overlapping neural substrates underlying these processes (Santarnecchi et al., 2021), 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') (Miyake et al., 2000). 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 (Santarnecchi et al., 2017b,a). Reasoning abilities, too, draw positive benefits from cognitive training (Park and Bischof, 2013; Yates et al., 2016; Ball et al., 2002).

4. 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 (Stavropoulos et al., 2020).

Shifting from pen and paper cognitive assessment and stimulation tools to computerized methods, besides potentially yielding better results (Djabelkhir et al., 2017) 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 (Liston and Stone, 2014), biomarkers derived from human voice (Wroge et al., 2018), the use of wearables such as actigraphs to track sleep and other health parameters (Martin and Hakim, 2011) and the recording of pen pressure or speed in drawing and writing tasks (Zham et al., 2017) 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.

5. 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 (Higgins-Chen et al., 2021). 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 (Stern et al., 2020). 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 (Nyberg et al., 2012).

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 (Roe et al., 2007; Snowdon, 2003), 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 (Stern, 2002; Menardi et al., 2018). 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 (Stern, 2013). Although potentially influenced by common lifestyle factors, cognitive reserve and brain maintenance/reserve are two separate, uncorrelated processes (Habeck et al., 2017).

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 (Kemppainen et al., 2008; Roe et al., 2007, 2008); 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 s é 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 (Berggren et al., 2018; Zahodne et al., 2011). Some questionnaires have been proposed, such as the Cognitive Reserve Index questionnaire, which take into account the multiple aspects of CR (Nucci et al., 2012); studies that have included social engagement and occupational attainments as components of CR have reported consistent findings of its beneficial impact on cognitive ageing (Li et al., 2021; Pettigrew and Soldan, 2019; Stern, 1994).

The inconsistency in defining and measuring CR has made the investigation into its neurobiological underpinnings particularly challenging (Stern et al., 2020), 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 (Snowdon, 2003), protein burden (Kemppainen et al., 2008; Roe et al., 2008) or cortical atrophy (Nyberg et al., 2021) 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 (Menardi et al., 2018; Roe et al., 2007); 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 (Menardi et al., 2018).

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 (Menardi et al., 2021; Santarnecchi et al., 2015). 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 (Barabási and Bonabeau, 2003). Although the precise genetic basis of CR and brain resilience have yet to be clarified, studies suggest the heritability of both (Lee, 2003; Menardi et al., 2021). Exploring the involvement of brain graph resilience as a correlate of CR might provide interesting insights into its neurobiology.

6. 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 (Fig. 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 (Weintraub et al., 2012) (Fig. 2b, dotted line). Memory impairment is typically the first reported symptom, although processing speed deficits seem to be the first to appear objectively (Daugherty et al., 2020), followed closely by executive and spatial deficits (Weintraub et al., 2012). Moreover, those crystallized functions which are spared in typical healthy ageing also become impaired in AD patients: semantic knowledge (McKhann et al., 2011), autobiographical memory (El Haj et al., 2015), automatic memory (Giffard et al., 2005) and emotion regulation (Weintraub et al., 2012) all endure significant deterioration with the progression of the disease.

On the contrary, individuals with high CR display particularly favourable outcomes (Fig. 2b, solid line). A recent longitudinal study conducted on 1697 individuals has assessed the influence of CR on cognitive trajectories (Li et al., 2021). 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.

7. Beneficial active interventions to promote healthy brain ageing

Active interventions to promote healthy brain ageing can prolong the cognitive healthspan (Krivanek et al., 2021) (Fig. 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

Table 1
Modifiable risk factors impacting healthy brain ageing.

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(Livingston et al., 2020). A systematic review including 13 longitudinal studies found that exposure to air pollutants was associated with increased dementia risk(Peters et al., 2019).
Smoking	Micro	Different systematic reviews confirm that active smoking increases the risk of dementia(Peters et al., 2008; Plassman et al., 2010). 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(Livingston et al., 2020). Multiple studies and meta-analyses have confirmed that a history of TBI increases the risk of dementia(Dams-O'Connor et al., 2016; Redelmeier et al., 2019), even reporting a two-fold surge(Redelmeier et al., 2019). 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(Sayed et al., 2013).
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(Shi et al., 2018). Because of the critical role afforded to sleep in protein and neurotoxic waste clearance(Xie et al., 2013), the primary proposed pathway revolves around diminished protein clearance function and subsequent pathological accumulation(Holth et al., 2017).
Obesity/weight	Micro/ Meso	Metabolic morbidity accelerates most of the hallmarks of brain ageing (e.g., neuroinflammation, impaired neuronal homeostasis)(Mattson and Arumugam, 2018). Moreover, studies have documented reduced grey matter volume(Li et al., 2022) and white matter integrity(Carbine, 2020) in multiple brain regions and reduced functional connectivity(Syan et al., 2021) 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(Kim et al., 2015). In humans, high stress levels were found to be associated with increased neural inflammation and diminished immune responses(Depp et al., 2010) as well as decreased brain volume and more prominent white matter lesions(Krivanek et al., 2021). In contrast hormesis, i.e., the steady

(*continued on next page*)

Table 1 (*continued*)

Risk Factor	Level	Evidence
		prolonged exposure to mild levels of stress, increases stress resilience and reduces vulnerability, with positive effects on cognitive ageing(Depp et al., 2010).
Diabetes	Micro/ Meso	Diabetes leads to vascular pathology(Alexandru, 2016) and to reduced hippocampal neurogenesis and neuroplasticity(Ho et al., 2013). 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(Plassman et al., 2010).
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(Armstrong et al., 2019).
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(Sabia et al., 2018) and increased dementia risk. Moreover, alcohol consumption is linearly negatively associated with grey and white matter volume (Rehm et al., 2019), 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(Krivanek et al., 2021).
Hypertension	Meso/ Macro	Midlife hypertension is associated with reduced brain volumes and increased white matter hyperintensity volume(Livingston et al., 2020).
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(Byers and Yaffe, 2011; Plassman et al., 2010). Proposed pathways include the direct effects of depression on stress hormones, neuronal growth factors and hippocampal atrophy(Bennett and A, 2014).
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(Krivanek et al., 2021). 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(Menardi et al., 2018; Stern and Barulli, 2019; Stern, 2021). Additionally, higher cognitive activity levels, especially in early life and in middle age, correlate with decreased Aβ deposition(Krivanek et al., 2021).

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 (Kane and Sinclair, 2019; Lu et al., 2020) 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 (Dellinger et al., 2017; Lautrup et al., 2019; Martens et al., 2018).

The brain's microstructure can be protected through several interventions. Among the best established of these are sleep interventions (Romanella et al., 2020). Disrupted sleep induces higher inflammation and decreased protein clearance (Krivanek et al., 2021), which can be minimized by promoting slow waves during non-REM sleep (Romanella et al., 2020). A randomized control study (RCT) has indeed demonstrated that treating sleep disorders partially mitigates negative effects on brain health (Ooms et al., 2014). 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 (Krivanek et al., 2021). RCTs demonstrate that stress reducing practices, such as yoga or meditation, lead to improved cognitive functioning in ageing (Wells et al., 2013; Innes et al., 2016). 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 (Plassman et al., 2010) and, because of the relevant impact depression has on stress and brain health and particularly on medial-temporal cortex integrity (Sheline et al., 1996), treating depression is likely to benefit processes of brain ageing (Krivanek et al., 2021).

Among the most robust effective interventions are physical exercise and adopting a healthy diet (Plassman et al., 2010). Exercise yields an increase in BDNF concentration (Choi et al., 2018) and insulin-like growth factor 1, promoting a healthier metabolism (Klimova et al., 2017; De la Rosa, 2020; Stillman et al., 2020), and induces better sleep patterns (Kline et al., 2021; Sewell et al., 2021) in all age groups (Stillman et al., 2020). Moreover, physical exercise interventions decrease overall AD pathology and brain volume loss, while strengthening the cardiovascular system and thus decreasing the connected risks (Krivanek et al., 2021). 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 (Paluch et al., 2022); trials testing exercise interventions show it has cascading effects, improving memory, mood, executive function and promoting brain plasticity (Fausto et al., 2022; Krivanek et al., 2021). Interestingly, a recent study (American Academy of Neurology, 2022) 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 (Levine et al., 2013), 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 (Roman et al., 2008), are widely accepted (Melzer et al., 2021). 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 (Krivanek et al., 2021); also, some emerging studies have even linked the Mediterranean diet with augmented telomere length (Crous-Bou et al., 2019). RCTs have shown that these diets induce improved global cognition and executive function (Klimova et al., 2017).

In the recent decades, several studies have focussed on behavioural interventions (Klimova et al., 2017) (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 (Wang et al., 2002), 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 (Carlson et al., 2008; Cohen-Mansfield et al., 2015), which is reflected in imaging studies as increased prefrontal and anterior cingulate cortex activation (Carlson et al., 2009) and an overall higher brain volume (Carlson et al., 2015).

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 (Gates et al., 2011), ranging from daily crosswords (Murphy et al., 2014) to structured multisession programs (Ball et al., 2002). 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 (Park and Bischof, 2013; Yates et al., 2016; Ball et al., 2002). Critically, cognitive training programs and memory training seem to be effective only if enacted before dementia onset (Kallio et al., 2018). The mechanisms underlying these beneficial effects are still unclear (Krivanek et al., 2021). 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 (Ledreux et al., 2019); other possible mechanisms include a reduction in AD pathology and maintained grey matter volume (Krivanek et al., 2021).

Although more rigorous RCTon cognitive training are still needed to clearly define its efficacy (Zehnder et al., 2009), 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 (Ngandu et al., 2015). 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 (Worldwide FinGer).

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 (Tatti et al., 2016), 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) (Antal et al., 2022; Tatti et al., 2016) or to modulate cortical connectivity (cortico-cortical paired associative stimulation, ccPAS) (Chiappini et al., 2018; Fiori et al., 2018; Koch, 2020; Turrini et al., 2023a,b). 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) (Salehinejad et al., 2020; Talar et al., 2022; Tatti et al., 2016). 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 (Tatti et al., 2016). 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 (Goldthorpe et al., 2020; Tatti et al., 2016).

8. 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.

CRediT authorship contribution statement

ST: conceptualization, Methodology, Visualization; Roles/Writing – original draft; Writing – review & editing; BW: Writing – review & editing, ME: Writing – review & editing, DZP: 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.

Financial support

This work was supported by the NIH via R01AG060981 from the National Institute of Aging and the ADDF-TreatFTD fund (GA201902–2017902) awarded to Emiliano Santarnecchi. This work was also supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) and grants from the Fondazione del Monte di Bologna e Ravenna (1402bis/2021), and Universidad Católica Del Maule (CDPDS2022) awarded to Alessio Avenanti.

Declaration of Competing Interest

D.A.S. is a consultant, inventor, board member, and in some cases an investor in Life Biosciences (developing reprogramming medicines), InsideTracker, Zymo, EdenRoc Sciences/Cantata/Dovetail/Metrobiotech, Caudalie, Galilei, Immetas, Animal Biosciences, Tally Health, and more. See https://sinclair. hms.harvard.edu/david-sinclairs-affiliations.

Data Availability

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

References

Aburto, J.M., Schöley, J., Kashnitsky, I., Zhang, L., Rahal, C., Missov, T.I., Kashyap, R., 2022. Quantifying impacts of the COVID-19 pandemic through life-expectancy losses: a population-level study of 29 countries. Int. J. Epidemiol. 51 (1), 63–74.

Akintola, A.A., van Heemst, D., 2015. Insulin, aging, and the brain: mechanisms and implications. Frontiers in endocrinology 6, 13.

Alexandru, N., et al., 2016. Vascular complications in diabetes: microparticles and microparticle associated microRNAs as active players dedicated to the 150th anniversary of the Romanian Academy. Biochem Biophys. Res Commun. 472, 1–10.

Alkerwi, A.A., Vernier, C., Sauvageot, N., Crichton, G.E., Elias, M.F., 2015. Demographic and socioeconomic disparity in nutrition: application of a novel Correlated Component Regression approach. BMJ Open 5 (5), e006814.

American Academy of Neurology. (2022, February 23). Do pets have a positive effect on your brain health? Study shows long-term pet ownership linked to slower decline in cognition over time. ScienceDaily. Retrieved May 2, 2023 from www.sciencedaily.com/releases/2022/02/220223210035.htm.

Antal, A., Luber, B., Brem, A.K., Bikson, M., Brunoni, A.R., Cohen Kadosh, R., Dubljević, V., Fecteau, S., Ferreri, F., Flöel, A., Hallett, M., Hamilton, R.H., Herrmann, C.S., Lavidor, M., Loo, C., Lustenberger, C., Machado, S., Miniussi, C., Moliadze, V., Nitsche, M.A., Rossi, S., Rossini, P.M., Santarnecchi, E., Seeck, M., Thut, G., Turi, Z., Ugawa, Y., Venkatasubramanian, G., Wenderoth, N., Wexler, A.,

Ziemann, U., Paulus, W., 2022. Non-invasive brain stimulation and neuroenhancement. Clin. Neurophysiol. Pract. 7, 146–165.
Arcos-burgos, M., Lopera, F., Sepulveda-falla, D., Mastronardi, C., 2019. Editorial neural plasticity during aging. Neural Plast. 2019, 1–3.
Armstrong, N.M., An, Y., Doshi, J., et al., 2019. Association of midlife hearing impairment with late-life temporal lobe volume loss. JAMA Otolaryngol. Head. Neck Surg. 145, 794.
Ball, K., Berch, D.B., Helmers, K.F., Jobe, J.B., L.M., Marsiske, M., Morris, J.N., Rebok, G. W., Smith, D.M., SL, T., Unverzagt, F.W., Willis, S.L., A.C., Group, T., 2002. for I. and V. E. S. effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 288, 2271–2281.
Baltes, P.B., 1980. Cohort effects in developmental psychology. Longitudinal research in the study of behavior and development, pp. 61–68.
Barabási, A.L., Bonabeau, E., 2003. Scale-free networks. Scientific american 288 (5), 60–69.
Barnes, C.A., 2003. Long-term potentiation and the ageing brain. Philos. Trans. R. Soc. B Biol. Sci. 358, 765–772.
Bekaert, S., De Meyer, T., 2005. Telomere attrition as ageing biomarker. Anticancer Res 25, 3011–3022.
Bennett, S., A, T., 2014. Depression and dementia: cause, consequence or coincidence. Maturitas 79, 184–190.
Benveniste, H., et al., 2019. The glymphatic system and waste clearance with brain aging: a review. Gerontology 65, 106–119.
Berggren, R., Nilsson, J., Lövdén, M., 2018. Education does not affect cognitive decline in aging: A Bayesian assessment of the association between education and change in cognitive performance. Frontiers in Psychology 9, 1138.
Bethlehem, R.A., Seidlitz, J., White, S.R., Vogel, J.W., Anderson, K.M., Adamson, C., Schaare, H.L., 2022. Brain charts for the human lifespan. Nature 604 (7906), 525–533.
Blasco, M.A., 2007. Telomere length, stem cells and aging. Nat. Chem. Biol. 3, 640–649.
Brown, W.R., Moody, D.M., Thore, C.R., Challa, V.R., Anstrom, J.A., 2007. Vascular dementia in leukoaraiosis may be a consequence of capillary loss not only in the lesions, but in normal-appearing white matter and cortex as well. J. Neurol. Sci. 257, 62–66.
Buckner, R.L., 2004. Memory and executive function in aging and ad: multiple factors that cause decline and reserve factors that compensate. Neuron 44, 195–208.
Bullitt, E., Zeng, D., Mortamet, B., Ghosh, A., Aylward, S.R., Lin, W., Smith, K., 2010. The effects of healthy aging on intracerebral blood vessels visualized by magnetic resonance angiography. Neurobiol. Aging 31 (2), 290–300.
Buzsáki, G., Wang, X.-J., 2012. Mechanisms of gamma oscillations. Annu. Rev. Neurosci. 35, 203–225.
Byers, A.L., Yaffe, K., 2011. Depression and risk of developing dementia. Nature Reviews Neurology 7 (6), 323–331.
Campbell, K.L., Grady, C.L., Ng, C., Hasher, L., 2012. Age differences in the frontoparietal cognitive control network: Implications for distractibility. Neuropsychologia 50 (9), 2212–2223.
Cansino, S., 2022. Brain connectivity changes associated with episodic recollection decline in aging: A review of fMRI studies. Frontiers in Aging Neuroscience 1225.
Carbine, K.A., et al., 2020. White matter integrity disparities between normal-weight and overweight/obese adolescents: an automated fiber quantification tractography study. Brain Imaging Behav. 14, 308–319.
Cardin, J.A., et al., 2009. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature 459, 663–667.
Carlson, M.C., Saczynski, J.S., Rebok, G.W., Seeman, T., Glass, T.A., McGill, S., Fried, L. P., 2008. Exploring the effects of an "everyday" activity program on executive function and memory in older adults. Experience Corps®. The Gerontologist 48 (6), 793–801.
Carlson, M.C., Kuo, J.H., Chuang, Y.F., Varma, V.R., Harris, G., Albert, M.S., Fried, L.P., 2015. Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. Alzheimer's & Dementia 11 (11), 1340–1348.
Carlson, M.C., Erickson, K.I., Kramer, A.F., Voss, MW, B., Mielke, N., McGill, M., Rebok, S., Seeman, G.W., T, F. L, 2009. Evidence for neurocognitive plasticity in at risk, older adults: the experience corps program. J. Gerontol. Biol. Sci. Med Sci. 64, 1275–1282.
Carlstrom, L.P., Eltanahy, A., Perry, A., Rabinstein, A.A., Elder, B.D., Morris, J.M., Burns, T.C., 2022. A clinical primer for the glymphatic system. Brain 145 (3), 843–857.
Carstensen, L.L., Fung, H.H., Charles, S.T., 2003. Socioemotional selectivity theory and the regulation of emotion in the second half of life. Motiv Emot. 27, 103–123.
Chetty, R., Stepner, M., Abraham, S., Lin, S., Scuderi, B., Turner, N., Cutler, D., 2016. The association between income and life expectancy in the United States, 2001-2014. JAMA 315 (16), 1750–1766.
Chiappini, E., Silvanto, J., Hibbard, P.B., Avenanti, A., Romei, V., 2018. Strengthening functionally specific neural pathways with transcranial brain stimulation. Curr. Biol. 28, R735–R736.
Choi, S.H., Bylykbashi, E., Chatila, Z.K., Lee, S.W., Pulli, B., Clemenson, G.D., Tanzi, R.E., 2018. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science 361 (6406), eaan8821.
Christensen, H., 2001. What cognitive changes can be expected with normal ageing? Aust. N. Z. J. Psychiatry 35, 768–775.
Christensen, K., Johnson, T.E., Vaupel, J.W., 2006. The quest for genetic determinants of human longevity: challenges and insights. Nat. Rev. Genet 436–448.
Cohen, R.A., Marsiske, M.M., Smith, G.E., 2019. Neuropsychology of aging. Handbook of clinical neurology 167, 149–180.
Cohen-Mansfield, J., Cohen, R., Buettner, L., E.N., Jakobovits, H., Rebok, G., Rotenberg-Shpigelman, S., S., Reporting, S., 2015. Interventions for older persons Study., memory difficulties: a randomized controlled pilot. Int J. Geriatr. Psychiatry 30, 478–486.
Crimmins, E.M., 2015. Lifespan and healthspan: past, present, and promise. The Gerontologist 55 (6), 901–911.
Crous-Bou, M., Molinuevo, J.L., & Sala-Vila, A. (2019). Plant-rich dietary patterns, plant foods and nutrients, and telomere length. *Advances in Nutrition*, *10*(Supplement_4), S296-S303.
Currais, A., Fischer, W., Maher, P., Schubert, D., 2017. Intraneuronal protein aggregation as a trigger for inflammation and neurodegeneration in the aging brain. The FASEB Journal 31 (1), 5.
Damoiseaux, J.S., 2017. Effects of aging on functional and structural brain connectivity. Neuroimage 160, 32–40.
Damoiseaux, J.S., Smith, S.M., Witter, M.P., Sanz-Arigita, E.J., Barkhof, F., Scheltens, P., Rombouts, S.A., 2009. White matter tract integrity in aging and Alzheimer's disease. Human brain mapping 30 (4), 1051–1059.
Dams-O'Connor, K., Guetta, G., Hahn-Ketter, A.E., Fedor, A., 2016. Traumatic brain injury as a risk factor for Alzheimer's disease: current knowledge and future directions. Neurodegener. Dis. Manag 6, 417.
Daugherty, A.M., Shair, S., Kavcic, V., Giordani, B., 2020. Slowed processing speed contributes to cognitive deficits in amnestic and non-amnestic mild cognitive impairment. Alzheimer's Dement. 16, 43163.
Davies, G., et al., 2015. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). Mol. Psychiatry 20, 183–192.
Day, J.J., Sweatt, J.D., 2010. DNA methylation and memory formation. Nat. Neurosci. 13, 1319–1323.
De Godoy, Alves, C.A.P.F., Alves, C.A.P.F., Saavedra, J.S.M., Studart-Neto, A., Nitrini, R., da Costa Leite, C., Bisdas, S., 2021. Understanding brain resilience in superagers: a systematic review. Neuroradiology 63, 663–683.
De la Rosa, A., et al., 2020. Physical exercise in the prevention and treatment of Alzheimer's disease. J. Sport Health Sci. 9, 394–404.
Debanne, D., Inglebert, Y., Russier, M., 2019. Plasticity of intrinsic neuronal excitability. Curr. Opin. Neurobiol. 54, 73–82.
Deery, H.A., Di Paolo, R., Moran, C., Egan, G.F., Jamadar, S.D., 2023. The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging. Psychophysiology 60 (1), e14159.
Dellinger, R.W., Santos, S.R., Morris, M., Evans, M., Alminana, D., Guarente, L., Marcotulli, E., 2017. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. npj Aging and Mechanisms of Disease 3 (1), 17.
Depp, C., Vahia, I.V., Jeste, D., 2010. Successful aging: focus on cognitive and emotional health. Annu Rev. Clin. Psychol. 6, 527–550.
Djabelkhir, L., Wu, Y.H., Vidal, J.S., Cristancho-Lacroix, V., Marlats, F., Lenoir, H., Rigaud, A.S., 2017. Computerized cognitive stimulation and engagement programs in older adults with mild cognitive impairment: comparing feasibility, acceptability, and cognitive and psychosocial effects. Clinical Interventions in Aging 1967.
Edler, M.K., Mhatre-Winters, I., Richardson, J.R., 2021. Microglia in aging and Alzheimer's disease: A comparative species review. Cells 10 (5), 1138.
El Haj, M., Antoine, P., Nandrino, J.L., Kapogiannis, D., 2015. Autobiographical memory decline in Alzheimer's disease, a theoretical and clinical overview. Ageing Res Rev. 23, 183–192.
Elia, M., 1992. Organ and tissue contribution to metabolic rate. Energy Metab. Tissue Determinants Cell. Corrolaries 61–77.
Ennis, W.J., Sui, A., Bartholomew, A., 2013. Stem cells and healing: impact on inflammation. Adv. Wound Care 2 (7), 369–378.
Fausto, B.A., Azimipour, S., Charles, L., Yarborough, C., Grullon, K., Hokett, E., Gluck, M. A., 2022. Cardio-dance exercise to improve cognition and mood in older African Americans: a propensity-matched cohort study. Journal of Applied Gerontology 41 (2), 496–505.
Fernando, M.S., Simpson, J.E., Matthews, F., Brayne, C., Lewis, C.E., Barber, R., Ince, P. G., 2006. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. Stroke 37 (6), 1391–1398.
Ferraro, K.F., Kemp, B.R., Williams, M.M., 2017. Diverse aging and health inequality by race and ethnicity. Innovation in aging 1 (1).
Ferreira, L.K., et al., 2016. Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. Cereb. Cortex 26 (9), 3851–3865.
Fiori, F., Chiappini, E., Avenanti, A., 2018. Enhanced action performance following TMS manipulation of associative plasticity in ventral premotor-motor pathway. Neuroimage 183, 847–858.
Fontana, L., Partridge, L., Longo, V.D., 2010. Extending healthy life span-from yeast to humans. Science 1979 (328), 321–326.
Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908 (1), 244–254.
Fromholt, P., Mortensen, D., Torpdahl, P., Bender, L., Larsen, P., Rubin, D., 2003. Life-narrative and word-cued autobiographical memories in centenarians: comparisons with 80-year-old control, depressed, and dementia groups. Memory 11 (1), 81–88.
Fukumoto, H., Asami-Odaka, A., Suzuki, N., Shimada, H., Ihara, Y., Iwatsubo, T., 1996. Amyloid beta protein deposition in normal aging has the same characteristics as that in Alzheimer's disease. Predominance of A beta 42 (43) and association of A beta 40 with cored plaques. The American journal of pathology 148 (1), 259.
Gates, N.J., Sachdev, P.S., Fiatarone Singh, M.A., Valenzuela, M., 2011. Cognitive and memory training in adults at risk of dementia: a systematic review. BMC Geriatr. 11 (1), 1–14.

Gefen, T., et al., 2019. Activated microglia in cortical white matter across cognitive aging trajectories. Front Aging Neurosci. 11, 1–8.
Gefen, T., Shaw, E., Whitney, K., Martersteck, A., Stratton, J., Rademaker, A., Rogalski, E., 2014. Longitudinal neuropsychological performance of cognitive SuperAgers. J. Am. Geriatr. Soc. 62 (8), 1598.
Giffard, B., Desgranges, B., Eustache, F., 2005. Semantic memory disorders in Alzheimers disease: clues from semantic priming effects. Curr. Alzheimer Res 2, 425–434.
Goldthorpe, R.A., Rapley, J.M., Violante, I.R., 2020. A systematic review of non-invasive brain stimulation applications to memory in healthy aging. Front Neurol. 11, 1247.
Gong, G., et al., 2009. Age- and gender-related differences in the cortical anatomical network. J. Neurosci. 29, 15684–15693.
Goodell, M.A., Rando, T.A., 2015. Stem cells and healthy aging. Science 1979 (350), 1199–1204.
Gorbunova, V., Seluanov, A., 2009. Coevolution of telomerase activity and body mass in mammals: from mice to beavers. Mech. Ageing Dev. 130, 3–9.
Gow, A.J., Bastin, M.E., Maniega, S.M., Hernández, M.C.V., Morris, Z., Murray, C., Wardlaw, J.M., 2012. Neuroprotective lifestyles and the aging brain: activity, atrophy, and white matter integrity. Neurology 79 (17), 1802–1808.
Green, D.R., Galluzzi, L., Kroemer, G., 2011. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science 333, 1109.
Gurland, B.J., Page, W.F., Bl, P., 2004. A twin study of the genetic contribution to age-related functional impairment. J. Gerontol. A Biol. Sci. Med. Sci. 59, 859–863.
Gutchess, A.H., Welsh, R.C., Hedden, T., Bangert, A., Minear, M., Liu, L.L., Park, D.C., 2005. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. Journal of cognitive neuroscience 17 (1), 84–96.
Habeck, C., Razlighi, Q., Gazes, Y., Barulli, D., Steffener, J., Stern, Y., 2017. Cognitive reserve and brain maintenance: orthogonal concepts in theory and practice. Cereb. Cortex 27 (8), 3962–3969.
Handing, E.P., Hayden, K.M., Leng, X.I., Kritchevsky, S.B., 2023. Predictors of cognitive and physical decline: Results from the Health Aging and Body Composition Study. Frontiers in Aging Neuroscience 15, 88.
Happé, F.G., Winner, E., Brownell, H., 1998. The getting of wisdom: theory of mind in old age. Dev. Psychol. 34, 358–362.
Harris, S.E., Deary, I.J., 2011. The genetics of cognitive ability and cognitive ageing in healthy older people. Trends Cogn. Sci. 15, 388–394.
Hawes, Z., Sokolowski, H.M., Ononye, C.B., Ansari, D., 2019. Neural underpinnings of numerical and spatial cognition: an fMRI meta-analysis of brain regions associated with symbolic number, arithmetic, and mental rotation. Neurosci. Biobehav Rev. 103, 316–336.
Hayano, M., Yang, J.H., Bonkowski, M.S., Amorim, J.A., Ross, J.M., Coppotelli, G., Sinclair, D.A., 2019. DNA break-induced epigenetic drift as a cause of mammalian aging. BioRxiv 808659.
Heckner, M.K., Cieslik, E.C., Eickhoff, S.B., Camilleri, J.A., Hoffstaedter, F., Langner, R., 2021. The aging brain and executive functions revisited: implications from meta-analytic and functional-connectivity evidence. Journal of cognitive neuroscience 33 (9), 1716–1752.
Hedden, T., Gabrieli, J.D., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nature reviews neuroscience 5 (2), 87–96.
Hermans, L., Leunissen, I., Pauwels, L., Cuypers, K., Peeters, R., Puts, N.A., Swinnen, S.P., 2018. Brain GABA levels are associated with inhibitory control deficits in older adults. Journal of Neuroscience 38 (36), 7844–7851.
Higgins-Chen, A.T., Thrush, K.L., Levine, M.E., 2021. Aging biomarkers and the brain. Semin Cell Dev. Biol. 116, 180–193.
Ho, N., Sommers, M.S., Lucki, I., 2013. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. Neurosci. Biobehav Rev. 37, 1346–1362.
Hofer, S.M., Sliwinski, M.J., 2006. Design and analysis of longitudinal studies on aging. *Handbook of the psychology of aging*. Academic Press, pp. 15–37.
Hoffman, L., Hofer, S.M., Sliwinski, M.J., 2011. On the confounds among retest gains and age-cohort differences in the estimation of within-person change in longitudinal studies: a simulation study. Psychol. Aging 26, 778–791.
Holth, J.K., Patel, T.K., Holtzman, D.M., 2017. Sleep in Alzheimer's disease–beyond amyloid. Neurobiol. Sleep. Circadian Rhythms 2, 4–14.
Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S.G., Croteau, D.L., Bohr, V.A., 2019. Ageing as a risk factor for neurodegenerative disease. Nature Reviews Neurology 15 (10), 565–581.
House, J.S., Lepkowski, J.M., Kinney, A.M., Mero, R.P., Kessler, R.C., Herzog, A.R., 1994. The social stratification of aging and health. J. Health Soc. Behav. 213–234.
Hwang, J.Y., Aromolaran, K.A., Zukin, R.S., 2017. The emerging field of epigenetics in neurodegeneration and neuroprotection. Nat. Rev. Neurosci. 18, 347–361.
Iaccarino, H.F., Singer, A.C., Martorell, A.J., Rudenko, A., Gao, F., Gillingham, T.Z., Tsai, L.H., 2016. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540 (7632), 230–235.
Innes, K.E., Selfe, T.K., Khalsa, D.S., Kandati, S., 2016. Effects of meditation versus music listening on perceived stress, mood, sleep, and quality of life in adults with early memory loss: a pilot randomized controlled trial. J. Alzheimer's Dis. 52, 1277–1298.
Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., Ikeda, M., 2017. Healthy and pathological brain aging: from the perspective of oscillations, functional connectivity, and signal complexity. Neuropsychobiology 75 (4), 151–161.
Jack, C.R., Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Kokmen, E., 1998. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology 51 (4), 993–999.
Jaskelioff, M., Muller, F.L., Paik, J.H., Thomas, E., Jiang, S., Adams, A.C., DePinho, R.A., 2011. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature 469 (7328), 102–106.
Johnson, A.A., Shokhirev, M.N., Wyss-Coray, T., Lehallier, B., 2020. Systematic review and analysis of human proteomics aging studies unveils a novel proteomic aging clock and identifies key processes that change with age. Ageing Res Rev. 60, 101070.
Kallio, E.-L., O¨hman, H., Hietanen, M., Soini, H., S., TE, Kautiainen, H., P.K., 2018. Effects of cognitive training on cognition and quality of life of older persons with dementia. J. Am. Geriatr. Soc. 66, 664–670.
Kane, A.E., Sinclair, D.A., 2019. Epigenetic changes during aging and their reprogramming potential. Crit. Rev. Biochem Mol. Biol. 54, 61–83.
Kearney, M.S., Levine, P.B., 2014. Income inequality, social mobility, and the decision to drop out of high school. National Bureau of Economic Research.
Kemppainen, N.M., Aalto, S., Karrasch, M., Någren, K., Savisto, N., Oikonen, V., Rinne, J. O., 2008. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 63 (1), 112–118.
Kim, E.J., Pellman, B., Kim, J.J., 2015. Stress effects on the hippocampus: a critical review. Learn. Mem. 22, 411–416.
Klimova, B., Valis, M., Kuca, K., 2017. Cognitive decline in normal aging and its prevention: a review on non-pharmacological lifestyle strategies. Clin. Inter. Aging 12, 903–910.
Kline, C.E., Hillman, C.H., Sheppard, B.B., Tennant, B., Conroy, D.E., Macko, R.F., Erickson, K.I., 2021. Physical activity and sleep: An updated umbrella review of the 2018 Physical Activity Guidelines Advisory Committee report. Sleep medicine reviews 58, 101489.
Koch, G., 2020. Cortico-cortical connectivity: the road from basic neurophysiological interactions to therapeutic applications. Exp. Brain Res 238, 1677–1684.
Kontis, V., Bennett, J.E., Mathers, C.D., Li, G., Foreman, K., Ezzati, M., 2017. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. The Lancet 389 (10076), 1323–1335.
Krivanek, T.J., Gale, S.A., McFeeley, B.M., Nicastri, C.M., Daffner, K.R., 2021. Promoting successful cognitive aging: a ten-year update. J. Alzheimer's Dis. 81, 871–920.
Kuhlen, R.S. (1961). Social change: a neglected factor in psychological studies of the life span.
La Voie, D., Light, L.L., 1994. Adult age differences in repetition priming: a meta-analysis. Psychol. Aging 9, 539–553.
Lautrup, S., Sinclair, D.A., Mattson, M.P., Fang, E.F., 2019. NAD+ in brain aging and neurodegenerative disorders. Cell Metab. 30, 630–655.
Ledreux, A., Håkansson, K., Carlsson, R., Kidane, M., Columbo, L., Terjestam, Y., Mohammed, A.K.H., 2019. Differential effects of physical exercise, cognitive training, and mindfulness practice on serum BDNF levels in healthy older adults: a randomized controlled intervention study. Journal of Alzheimer's Disease 71 (4), 1245–1261.
Lee, J.H., 2003. Genetic evidence for cognitive reserve: variations in memory and related cognitive functions, 2003 J. Clin. Exp. Neuropsychol. 25 (5), 594–613.
Leenders, K.L., Perani, D., Lammertsma, A.A., Heather, J.D., Buckingham, P., Jones, T., Frackowiak, R.S.J., 1990. Cerebral blood flow, blood volume and oxygen utilization: normal values and effect of age. Brain 113 (1), 27–47.
Levine, G.N., Allen, K., Braun, L.T., Christian, H.E., Friedmann, E., Taubert, K.A., Lange, R.A., 2013. Pet ownership and cardiovascular risk: a scientific statement from the American Heart Association. Circulation 127 (23), 2353–2363.
Lewis, C.M., Vassos, E., 2020. Polygenic risk scores: from research tools to clinical instruments. Genome Med 12, 1–11.
Li, L., Yu, H., Zhong, M., Liu, S., Wei, W., Meng, Y., Wang, Q., 2022. Gray matter volume alterations in subjects with overweight and obesity: Evidence from a voxel-based meta-analysis. Frontiers in Psychiatry 13.
Li, X., Song, R., Qi, X., Xu, H., Yang, W., Kivipelto, M., Xu, W., 2021. Influence of cognitive reserve on cognitive trajectories: role of brain pathologies. Neurology 97 (17), e1695–e1706.
Lindahl, T., 1993. Instability and decay of the primary structure of DNA. nature 362 (6422), 709–715.
Liston, D.B., Stone, L.S., 2014. Oculometric assessment of dynamic visual processing. Journal of vision 14 (14), 12.
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Mukadam, N., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396 (10248), 413–446.
López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194.
Lövdén, M., Schmiedek, F., Kennedy, K.M., Rodrigue, K.M., Lindenberger, U., Raz, N., 2013. Does variability in cognitive performance correlate with frontal brain volume? Neuroimage 64, 209–215.
Lu, Y., Brommer, B., Tian, X., Krishnan, A., Meer, M., Wang, C., Sinclair, D.A., 2020. Reprogramming to recover youthful epigenetic information and restore vision. Nature 588 (7836), 124–129.
Luo, X.G., Ding, J.Q., Chen, S.Di, 2010. Microglia in the aging brain: relevance to neurodegeneration. Mol. Neurodegener. 5, 1–9.
Lynch, M.A., 1998. Age-related impairment in long-term potentiation in hippocampus: a role for the cytokine, interleukin-1β? Prog. Neurobiol. 56, 571–589.
Mahncke, H.W., Bronstone, A., Merzenich, M.M., 2006. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog. Brain Res. 157, 81–109.
Marner, L., Nyengaard, J.R., Tang, Y., Pakkenberg, B., 2003. Marked loss of myelinated nerve fibers in the human brain with age. J. Comp. Neurol. 462, 144–152.
Martens, C.R., Denman, B.A., Mazzo, M.R., Armstrong, M.L., Reisdorph, N., McQueen, M. B., Seals, D.R., 2018. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. Nature communications 9 (1), 1286.

Martin, J.L., Hakim, A.D., 2011. Wrist actigraphy. Chest 139 (6), 1514–1527.
Mattson, M.P., Arumugam, T.V., 2018. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab. 27, 1176–1199.
Maynard, S., Fang, E.F., Scheibye-Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA damage, DNA repair, aging, and neurodegeneration. Cold Spring Harb. Perspect. Med 5 (10), a025130.
McArdle, J.J., Ferrer-Caja, E., Hamagami, F., Woodcock, R.W., 2002. Comparative longitudinal structural analyses of the growth and decline of multiple intellectual abilities over the life span. Developmental psychology 38 (1), 115.
McCartney, D.L., Hillary, R.F., Conole, E.L., Banos, D.T., Gadd, D.A., Walker, R.M., Marioni, R.E., 2022. Blood-based epigenome-wide analyses of cognitive abilities. Genome biology 23 (1), 26.
McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, Kawas, C.H., Kawas, C.H., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia 7 (3), 263–269.
Melzer, T.M., Manosso, L.M., Yau, S.Y., Gil-Mohapel, J., Brocardo, P.S., 2021. In pursuit of healthy aging: effects of nutrition on brain function. International journal of molecular sciences 22 (9), 5026.
Menardi, A., Pascual-Leone, A., Fried, P.J., Santarnecchi, E., 2018. The role of cognitive reserve in Alzheimer's disease and aging: a multi-modal imaging review. J. Alzheimer's Dis. 66, 1341–1362.
Menardi, A., Reineberg, A.E., Vallesi, A., Friedman, N.P., Banich, M.T., Santarnecchi, E., 2021. Heritability of brain resilience to perturbation in humans. NeuroImage 235, 118013.
Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. Cognitive psychology 41 (1), 49–100.
Mohai, P., Pellow, D., Roberts, J.T., 2009. Environmental justice. Annu Rev. Environ. Resour. 34, 405–430.
Murphy, M., O'Sullivan, K., Kelleher, K.G., 2014. Daily crosswords improve verbal fluency: a brief intervention study. International journal of geriatric psychiatry 29 (9), 915–919.
Murty, D.V., Manikandan, K., Kumar, W.S., Ramesh, R.G., Purokayastha, S., Javali, M., Ray, S., 2020. Gamma oscillations weaken with age in healthy elderly in human EEG. NeuroImage 215, 116826.
Neuner, S.M., Ding, S., Kaczorowski, C.C., 2019. Knockdown of heterochromatin protein 1 binding protein 3 recapitulates phenotypic, cellular, and molecular features of aging. Aging Cell 18.
Ng, K.K., Lo, J.C., Lim, J.K.W., Chee, M.W.L., Zhou, J., 2016. Reduced functional segregation between the default mode network and the executive control network in healthy older adults: a longitudinal study. Neuroimage 133, 321–330.
Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Kivipelto, M., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385 (9984), 2255–2263.
Nilsson, L.G., BÄCkman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, G., Winblad, B., 1997. The Betula prospective cohort study: Memory, health, and aging. Aging, Neuropsychology, and Cognition 4 (1), 1–32.
Niraula, A., Sheridan, J.F., Godbout, J.P., 2017. Microglia priming with aging and stress. Neuropsychopharmacology 42, 318–333.
Noël, R.A., 2018. Race, economics, and social status.
Nucci, M., Mapelli, D, M.S., 2012. Cognitive reserve index questionnaire (CRIq): a new instrument for measuring cognitive reserve. Aging Clin. Exp. Res 24, 218–226.
Nyberg, L., Bäckman, L., Erngrund, K., Olofsson, U., Nilsson, L.G., 1996. Age differences in episodic memory, semantic memory, and priming: relationships to demographic, intellectual, and biological factors. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 51, 234–240.
Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends Cogn. Sci. 16 (5), 292–305.
Nyberg, L., Magnussen, F., Lundquist, A., Baaré, W., Bartrés-Faz, D., Bertram, L., Fjell, A. M., 2021. Educational attainment does not influence brain aging. Proceedings of the National Academy of Sciences 118 (18), e2101644118.
O'Donoghue, M.C., Murphy, S.E., Zamboni, G., Nobre, A.C., Mackay, C.E., 2018. APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: a review. Cortex 104, 103–123.
Obernier, K., Alvarez-Buylla, A., 2019. Neural stem cells: origin, heterogeneity and regulation in the adult mammalian brain. Development 146 (4), dev156059.
Ooms, S., Overeem, S., Besse, K., Rikkert, M.O., Verbeek, M., Claassen, J.A., 2014. Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: a randomized clinical trial. JAMA neurology 71 (8), 971–977.
Paluch, A.E., Bajpai, S., Bassett, D.R., Carnethon, M.R., Ekelund, U., Evenson, K.R., Fulton, J.E., 2022. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. The Lancet Public Health 7 (3), e219–e228.
Pantoni, L., 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 9, 689–701.
Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev. Psychol. 60, 173–196.
Park, D.C., Bischof, G.N., 2013. The aging mind: neuroplasticity in response to cognitive training. Dialog-. Clin. Neurosci. 15, 109–119.
Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K., 2002. Models of visuospatial and verbal memory across the adult life span. Psychology and aging 17 (2), 299.
Partridge, L., Deelen, J., Slagboom, P.E., 2018. Facing up to the global challenges of ageing. Nature 561, 45–56.
Penke, L., Maniega, S.M., Murray, C., Gow, A.J., Hernández, M.C.V., Clayden, J.D., Deary, I.J., 2010. A general factor of brain white matter integrity predicts information processing speed in healthy older people. Journal of Neuroscience 30 (22), 7569–7574.
Peters, R., 2006. Ageing and the brain. Post. Med J. 82, 84–88.
Peters, R., Poulter, R., Warner, J., Beckett, N., Burch, L., Bulpitt, C., 2008. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC geriatrics 8, 1–7.
Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., KJ, A., 2019. Air pollution and dementia: a systematic review. J. Alzheimers Dis. 70, S145–S163.
Pettigrew, C., Soldan, A., 2019. Defining cognitive reserve and implications for cognitive aging. Curr. Neurol. Neurosci. Rep. 19, 1.
Plassman, B.L., Williams, J.W., Burke, J.R., Holsinger, T., Benjamin, S., 2010. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann. Intern Med 153, 182–193.
Powers, E.T., Morimoto, R.I., Dillin, A., Kelly, J.W., Balch, W.E., 2009. Biological and chemical approaches to diseases of proteostasis deficiency. Annu Rev. Biochem 78, 959–991.
Rabbitt, P., Lunn, M., Ibrahim, S., McInnes, L., 2009. Further analyses of the effects of practice, dropout, sex, socio-economic advantage, and recruitment cohort differences during the University of Manchester longitudinal study of cognitive change in old age. Q. J. Exp. Psychol. 62, 1859–1872.
Redelmeier, D.A., Manzoor, F., Thiruchelvam, D., 2019. Association between statin use and risk of dementia after a concussion. JAMA Neurol. 76, 887–896.
Rehm, J., Hasan, O.S.M., Black, S.E., Shield, K.D., Schwarzinger, M., 2019. Alcohol use and dementia: a systematic scoping review 11 medical and health sciences 1117 public health and health services. Alzheimers Res Ther. 11, 1–11.
Ritchie, S.J., Hill, W.D., Marioni, R.E., Davies, G., Hagenaars, S.P., Harris, S E., . & Deary, I.J. (2020). Polygenic predictors of age-related decline in cognitive ability. *Molecular Psychiatry*, *25*(10), 2584-2598.
Rodier, F., Campisi, J., 2011. Four faces of cellular senescence. J. Cell Biol. 192, 547–556.
Roe, C.M., Xiong, C., Miller, JP, M.J., 2007. Education and Alzheimer disease without dementia: Support for the cognitive reserve hypothesis. Neurology 68, 223–228.
Roe, C.M., Mintun, M.A., D'Angelo, G., Xiong, C., Grant, E.A., Morris, J.C., 2008. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11–labeled Pittsburgh Compound B uptake. Archives of neurology 65 (11), 1467.
Roman, B., Carta, L., Angel, M., 2008. Effectiveness of the Mediterranean diet in the elderly. Clin. Inter. Aging 3 (1), 97.
Romanella, S.M., Roe, D., Paciorek, R., Cappon, D., Ruffini, G., Menardi, A., Santarnecchi, E., 2020. Sleep, noninvasive brain stimulation, and the aging brain: challenges and opportunities. Ageing research reviews 61, 101067.
Rowe, J.W., Kahn, R.L., 1987. Human aging: usual and successful. Science 237 (4811), 143–149.
Rowe, J.W., Kahn, R.L., 1997. Successful aging. Gerontologist 37 (4), 433–440.
Rubin, David C. "Autobiographical memory and aging." (2000): 131-149.
Sabia, S., Fayosse, A., Dumurgier, J., Dugravot, A., Akbaraly, T., Britton, A., … Singh-Manoux, A., 2018. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study bmj, 362.
Salehinejad, M.A., Nejati, V., Mosayebi-Samani, M., Mohammadi, A., Wischnewski, M., Kuo, M.F., Avenanti, A., Vicario, C.M., Nitsche, M.A., 2020. Transcranial Direct Current Stimulation in ADHD: A Systematic Review of Efficacy, Safety, and Protocol-induced Electrical Field Modeling Results. Neurosci. Bull. 36 (10), 1191–1212.
Salim, S., 2017. Oxidative stress and the central nervous system. J. Pharmacol. Exp. Ther. 360, 201–205.
Salminen, A., Kaarniranta, K., Kauppinen, A., 2012. Inflammaging: disturbed interplay between autophagy and inflammasomes. Aging 4, 166–175.
Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103 (3), 403.
Salthouse, T.A., 2009. When does age-related cognitive decline begin? Neurobiol. Aging 30, 507–514.
Salthouse, T.A., 2010. Selective review of cognitive aging. J. Int. Neuropsychol. Soc. 16, 754–760.
Salthouse, T.A., 2011. Cognitive correlates of cross-sectional differences and longitudinal changes in trail making performance. J. Clin. Exp. Neuropsychol. 33, 242–248.
Salthouse, T.A., 2014. Correlates of cognitive change. J. Exp. Psychol. Gen. 143, 1026–1048.
Salthouse, T.A., Ferrer-Caja, E., 2003. What needs to be explained to account for age-related effects on multiple cognitive variables? Psychol. Aging 18, 91–110.
Salthouse, T.A., Davis, H.P., 2006. Organization of cognitive abilities and neuropsychological variables across the lifespan. Dev. Rev. 26, 31–54.
Salthouse, T.A., Schroeder, D.H., Ferrer, E., 2004. Estimating retest effects in longitudinal assessments of cognitive functioning in adults between 18 and 60 years of age. Dev. Psychol. 40, 813–822.
Sánchez-Izquierdo, M., Fernández-Ballesteros, R., 2021. Cognition in healthy aging. Int J. Environ. Res Public Health 18, 1–30.
Santarnecchi, E., Rossi, S., Rossi, A., 2015. The smarter, the stronger: intelligence level correlates with brain resilience to systematic insults. Cortex 64, 293–309.
Santarnecchi, E., Emmendorfer, A., Pascual-Leone, A., 2017. Dissecting the parieto-frontal correlates of fluid intelligence: a comprehensive ALE meta-analysis study. Intelligence 63, 9–28.
Santarnecchi, E., Emmendorfer, A., Tadayon, S., Rossi, S., Rossi, A., Pascual-Leone, A., 2017. Network connectivity correlates of variability in fluid intelligence performance. Intelligence 65, 35–47.

Santarnecchi, E., Momi, D., Mencarelli, L., Plessow, F., Saxena, S., Rossi, S., Pascual-Leone, A., 2021. Overlapping and dissociable brain activations for fluid intelligence and executive functions. Cognitive, Affective, & Behavioral Neuroscience 21 (2), 327–346.
Sayed, N., Culver, C., Dams-O'Connor, K., Hammond, F., Diaz-Arrastia, R., 2013. Clinical phenotype of dementia after traumatic brain injury. J. Neurotrauma 30, 1117–1122.
Scahill, R.I., Frost, C., Jenkins, R., Whitwell, J.L., Rossor, M.N., Fox, N.C., 2003. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch. Neurol. 60 (7), 989–994.
Schaie, K.W., Willis, S.L., Caskie, G.I., 2004. The Seattle longitudinal study: Relationship between personality and cognition. Aging Neuropsychology and Cognition 11 (2–3), 304–324.
Schaie, K.W. (2008). Historical processes and patterns of cognitive aging.
Sewell, K.R., Erickson, K.I., Rainey-Smith, S.R., Peiffer, J.J., Sohrabi, H.R., Brown, B.M., 2021. Relationships between physical activity, sleep and cognitive function: A narrative review. Neuroscience & Biobehavioral Reviews 130, 369–378.
Sheline, Y.I., Wang, P.W., Gado, M.H., Csernansky, J.G., Vannier, M.W., 1996. Hippocampal atrophy in recurrent major depression. Proc. Natl. Acad. Sci. 93 (9), 3908–3913.
Shi, L., Chen, S.J., Ma, M.Y., Bao, Y.P., Han, Y., Wang, Y.M., Lu, L., 2018. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. Sleep medicine reviews 40, 4–16.
Smith, E.E., O'Donnell, M., Dagenais, G., Lear, S.A., Wielgosz, A., Sharma, M., Pure Investigators, 2015. Early cerebral small vessel disease and brain volume, cognition, and gait. Annals of neurology 77 (2), 251.
Smith, J., Maas, I., Mayer, K.U., Helmchen, H., Steinhagen-Thiessen, E., Baltes, P.B., 2002. Two-wave longitudinal findings from the Berlin Aging Study: Introduction to a collection of articles. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 57 (6), 471–P473.
Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Sherwood, A., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosomatic medicine 72 (3), 239.
Snowdon, D.A., 2003. Healthy aging and dementia: findings from the nun study. Ann. Intern Med 139, 450.
Spreng, R.N., Stevens, W.D., Viviano, J.D., Schacter, D.L., 2016. Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. Neurobiol. Aging 45, 149–160.
Stavropoulos, T.G., Papastergiou, A., Mpaltadoros, L., Nikolopoulos, S., Kompatsiaris, I., 2020. IoT wearable sensors and devices in elderly care: a literature review. Sensors 20, 2826.
Steptoe, A., Zaninotto, P., 2020. Lower socioeconomic status and the acceleration of aging: an outcome-wide analysis. Proc. Natl. Acad. Sci. 117 (26), 14911–14917.
Stern, Y., 1994. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA: J. Am. Med. Assoc. 271, 1004.
Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460.
Stern, Y., 2013. Cognitive reserve in ageing. Lancet Neurol. 11, 1006–1012.
Stern, Y., 2021. How can cognitive reserve promote cognitive and neurobehavioral health? Arch. Clin. Neuropsychol. 36, 1291–1295.
Stern, Y., Barulli, D., 2019. Cognitive reserve. Handbook of clinical neurology 167, 181–190.
Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., . & Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16* (9), 1305-1311.
Stillman, C.M., Esteban-Cornejo, I., Brown, B., Bender, C.M., Erickson, K.I., 2020. Effects of exercise on brain and cognition across age groups and health states. Trends Neurosci. 43, 533–543.
Sullivan, E.V., Pfefferbaum, A., 2006. Diffusion tensor imaging and aging. Neurosci. Biobehav Rev. 30, 749–761.
Syan, S.K., McIntyre-Wood, C., Minuzzi, L., Hall, G., McCabe, R.E., MacKillop, J., 2021. Dysregulated resting state functional connectivity and obesity: A systematic review. Neuroscience & Biobehavioral Reviews 131, 270–292.
Talar, K., Vetrovsky, T., van Haren, M., Négyesi, J., Granacher, U., Váczi, M., Martín-Arévalo, E., Del Olmo, M.F., Kałamacka, E., Hortobágyi, T., 2022. The effects of aerobic exercise and transcranial direct current stimulation on cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. Ageing Res. Rev. 81, 101738.
Tarumi, T., Zhang, R., 2018. Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. J. Neurochem 595–608.
Tatti, E., Rossi, S., Innocenti, I., Rossi, A., Santarnecchi, E., 2016. Non-invasive brain stimulation of the aging brain: state of the art and future perspectives. Ageing Res Rev. 29, 66–89.
Thompson, J.M., Nuerk, H.C., Moeller, K., Cohen Kadosh, R., 2013. The link between mental rotation ability and basic numerical representations. Acta Psychol. 144, 324–331.
Tidwell, T.R., Søreide, K., Hagland, H.R., 2017. Aging, metabolism, and cancer development: from Peto's paradox to the Warburg effect. Aging Dis. 8, 662–676.
Touroutoglou, A., Zhang, J., Andreano, J.M., Dickerson, B.C., Barrett, L.F., 2018. Dissociable effects of aging on salience subnetwork connectivity mediate age-related changes in executive function and affect. Front Aging Neurosci. 10, 1–11.
Treusch, S., Hamamichi, S., Goodman, J.L., Matlack, K.E., Chung, C.Y., Baru, V., Lindquist, S., 2011. Functional links between Aβ toxicity, endocytic trafficking, and Alzheimer's disease risk factors in yeast. Science 334 (6060), 1241–1245.
Tucker-Drob, E.M., De la Fuente, J., Köhncke, Y., Brandmaier, A.M., Nyberg, L., Lindenberger, U., 2022. A strong dependency between changes in fluid and crystallized abilities in human cognitive aging. Science Advances 8 (5), eabj2422.
Tucker-Drob, E.M., 2011. Global and domain-specific changes in cognition throughout adulthood. Dev. Psychol. 47, 331–343.
Tucker-Drob, E.M., Salthouse, T.A., 2008. Adult age trends in the relations among cognitive abilities. Psychol. Aging 23, 453–460.
Tucker-Drob, E.M., Brandmaier, A.M., Lindenberger, U., 2019. Coupled cognitive changes in adulthood: a meta-analysis. Psychol. Bull. 145, 273–301.
Turrini, S., Fiori, F., Chiappini, E., Lucero, B., Santarnecchi, E., Avenanti, A., 2023b. Cortico-cortical paired associative stimulation (ccPAS) over premotor-motor areas affects local circuitries in the human motor cortex via Hebbian plasticity. Neuroimage 271, 120027.
Turrini, S., Bevacqua, N., Cataneo, A., Chiappini, E., Fiori, F., Candidi, M., Avenanti, A., 2023a. Transcranial cortico-cortical paired associative stimulation (ccPAS) over ventral premotor-motor pathways enhances action performance and corticomotor excitability in young adults more than in elderly adults. Front. Aging Neurosci. 15, 1119508.
Vidal-Piñeiro, D., Valls-Pedret, C., Fernández-Cabello, S., Arenaza-Urquijo, E.M., Sala-Llonch, R., Solana, E., Bartrés-Faz, D., 2014. Decreased default mode network connectivity correlates with age-associated structural and cognitive changes. Front Aging Neurosci. 6 (256).
Wang, H.-X., Karp, A., Winblad B, F.L., 2002. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen Project. Am. J. Epidemiol. 155, 1081–1087.
Weintraub, S., Wicklund, A.H., Salmon, D.P., 2012. The neuropsychological profile of Alzheimer disease. Cold Spring Harbor perspectives in medicine 2 (4), a006171.
Wells, R.E., Kerr, C.E., Wolkin, J., Dossett, M., Davis, R.B., Walsh, J., Yeh, G., 2013. Meditation for adults with mild cognitive impairment: a pilot randomized trial. Journal of the American Geriatrics Society 61 (4), 642.
WHO. WHO definition of healthy aging. ⟨https://www.who.int/news-room/questions-and-answers/item/healthy-ageing-and-functional-ability⟩.
Worldwide FinGer. ⟨https://www.alz.org/wwfingers/overview.asp⟩.
Wroge, T.J., Özkanca, Y., Demiroglu, C., Si, D., Atkins, D.C., Ghomi, R.H., 2018. Parkinson's disease diagnosis using machine learning and voice. 2018 IEEE Signal Process. Med. Biol. Symp. 1–7.
Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. science 342 (6156), 373–377.
Yates, L.A., Ziser, S., Spector, A, O.M., 2016. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. Int Psychogeriatr. 28, 1791–1806.
Yousefzadeh, M., Henpita, C., Vyas, R., Soto-Palma, C., Robbins, P., Niedernhofer, L., 2021. DNA damage—how and why we age? Elife 10, e62852.
Zacharopoulos, G., Sella, F., Cohen Kadosh, K., Hartwright, C., Emir, U., Cohen Kadosh, R., 2021. Predicting learning and achievement using GABA and glutamate concentrations in human development. PLoS biology 19 (7), e3001325.
Zahodne, L.B., Glymour, M.M., Sparks, C., Bontempo, D., Dixon, R.A., MacDonald, S.W., Manly, J.J., 2011. Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. Journal of the International Neuropsychological Society 17 (6), 1039–1046.
Zehnder, F., Martin, M., Altgassen, M., Clare, L., 2009. Memory training effects in old age as markers of plasticity: a meta-analysis. Restor. Neurol. Neurosci. 27 (5), 507–520.
Zham, P., Kumar, D.K., Dabnichki, P., Poosapadi Arjunan, S., Raghav, S., 2017. Distinguishing different stages of Parkinson's disease using composite index of speed and pen-pressure of sketching a spiral. Front Neurol. 435.
Zhao, T., Cao, M., Niu, H., Zuo, X.N., Evans, A., He, Y., Shu, N., 2015. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. Human brain mapping 36 (10), 3777–3792.
Zhu, X.H., Lu, M., Lee, B.Y., Ugurbil, K., Chen, W., 2015. In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. Proceedings of the National Academy of Sciences 112 (9), 2876–2881.