



HAL
open science

Normal ageing of the brain: Histological and biological aspects

T. Teissier, E. Boulanger, V. Deramecourt

► **To cite this version:**

T. Teissier, E. Boulanger, V. Deramecourt. Normal ageing of the brain: Histological and biological aspects. *Revue Neurologique*, 2020, 176, pp.649 - 660. 10.1016/j.neurol.2020.03.017 . hal-03493400

HAL Id: hal-03493400

<https://hal.science/hal-03493400v1>

Submitted on 17 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Normal ageing of the brain: histological and biological aspects

Thibault TEISSIER¹, Eric BOULANGER^{1,2}, Vincent DERAMECOURT^{3,4}

¹ Univ. Lille, CHU Lille, Inserm, Institut Pasteur de Lille, U1167 - RID-AGE - Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Equipe « de l'Inflammation au Vieillissement, F-59000, Lille, France

² CHU Lille - Pôle de Gériatrie, F-59000, Lille, France

³ Univ. Lille, Inserm, CHU Lille, UMR-S 1172 « Alzheimer et Tauopathies », Centre Mémoire de Ressources et de Recherche, Labex DISTALZ, F-59000 Lille, France

⁴ CHU Lille - Pôle de Neurologie, F-59000, Lille, France

Abstract

All the hallmarks of ageing are observed in the brain, and its cells, especially neurons, are characterized by their remarkably long lifetime. Like any organ or system, the brain is exposed to ageing processes which affect molecules, cells, blood vessels, gross morphology and, uniquely for this organ, cognition. The preponderant cerebral structures are characterized by the cellular processes of neurons and glial cells and while the quantity of cerebral interstitial fluid is limited, it is now recognized as playing a crucial role in maintaining cerebral homeostasis. Most of our current knowledge of the ageing brain derives from studies of neurodegenerative disorders. It is interesting to note that common features of these disorders, like Tau, phosphoTau and amyloid peptide accumulation, can begin relatively early in life as a result of physiological ageing and are present in subclinical cases while also being used as early-stage markers of neurodegenerative diseases in progression.

In this article, we review tissue and cellular modifications in the ageing brain. Commonly described macroscopic, microscopic and vascular changes that in the ageing brain are contrasted with those seen in neurodegenerative contexts. We also review the molecular changes that occur with age in the brain, such as modifications in gene expression, insulin/insulin-like growth factor 1 signalling dysfunction, post-translational protein modifications, mitochondrial dysfunction, autophagy and calcium conductance changes.

1. Introduction

The histological architecture of the brain is remarkably complex. Grey and white brain matter are both characterised by the processes of tightly-interspersed neurons and glial cells. Despite its small volume, the interstitial fluid is now known to play a crucial role in maintaining the homeostasis of such a complex cellular system. Its composition is highly regulated by the blood-brain barrier. It also plays an important role in protecting the brain against neurotoxic compounds and in clearing metabolic and peptidic waste, such as the amyloid peptide, from the brain to perivascular spaces. Thus, it is sometimes considered to be an equivalent of the lymphatic system in the central nervous system, and has come to be known as the glymphatic system [1].

Brain cells, and especially neurons, are remarkable for their long lifetime. Once mature, most of our neurons last our entire lifetime and show a high potential for plasticity in order to continuously modulate and adapt their complex synaptic network to changing conditions.

Like any organ or system, the brain is exposed to the ageing process which affects molecules, cells, blood vessels, gross morphology. Unlike other organs, however, the ageing process in the brain can significantly affect cognition. Changes in the brain with age have been studied since the 19th century – the exact nature and precise mechanisms of these changes nevertheless remain, for the most part, poorly defined. Furthermore, it remains difficult to define the boundary between “normal” changes due to ageing and the early stages of common, neurodegenerative diseases such as Alzheimer’s disease (AD) seen in elderly people.

In this article, we review the macroscopic, structural and molecular changes that occur with ageing, the main neuropathological lesions commonly found in normal ageing brains, and discuss how ageing affects neuroplasticity.

2. Tissue and cell modifications in the ageing brain

2.1. Macroscopic brain changes with age

The volume and the weight of the human brain exhibits significant interindividual variability. There also exists a cohort bias since the mean weight of the human brain has significantly increased over the 20th century (about 1g/y) [2]. Early post-mortem studies, later confirmed by neuroimaging longitudinal studies, have shown that brain weight loss is very subtle between 20 and 60 years of age (about 0.1% per year) [3]. The progressive atrophy may be more rapid thereafter, particularly over the age of 70 [4], [5], with an annual rate of weight loss between 2 and 5%. The reasons for this progressive loss of brain weight with age are not clear. The most commonly reported explanations are the decline in volume of pyramidal neurons (rather than their number or density) and a decrease in their dendritic and axonal arborizations [6]. This decrease is quite diffuse in white matter, but the shrinkage of grey matter is less uniform with the frontoparietal cortex more affected than the temporo-occipital [7]. As a consequence of this reduced brain volume, the ventricular system expands and the subarachnoid space enlarges (Fig. 1A and B).

2.2. Microscopic brain changes with age

The issue of neuronal loss has long been a matter of controversy. Initial studies, from the 1950s, overestimated the loss of neurons with age because their density was only evaluated in two-dimensions – the cerebral cortex and hippocampus were thought to be particularly affected. However, different conclusions were arrived at with the use of modern, stereologically-based quantification in three dimensions [8]–[11]. Neuronal loss with ageing is now considered as either undetectable or not exceeding 10% over our life span [12], [13]. In some parts of the brain such as the locus coeruleus (LC), however, up to 25% of LC neurons are lost in the elderly (between the fourth and ninth decade) [14]. Grey matter volume also significantly reduces over time, with the most severe losses in the insula, superior parietal gyri, central sulci, and cingulate sulci while amygdala, hippocampi, and entorhinal cortex are relatively well preserved [15], [16]. However, grey matter shrinkage does not necessarily result from neurodegeneration: it is rather suggested that it is mainly caused by extensive dendritic regression [17]. A decline in white matter volume and integrity has also been reported [18]–[20], notably in the prefrontal cortex [21]. Therefore, normal cellular brain ageing is characterized more by subtle changes than a large-scale loss of cells. In the hippocampus, dendritic extents may increase in the dentate gyrus [22] while remaining stable in the 1 and 3 areas of the cornu ammonis (CA) and in the subiculum [23]–[25]. Similarly, no change in spines' density with age has been reported in the human hippocampus [26], [27]. On the other hand, frontal cortex and cingulate pyramidal neurons show a decrease in dendritic branching in rats [28], [29] which has also been found in the human medial prefrontal cortex [30]. In areas 10 and 18 of the human cortex, a 46% reduction in spine number and density has been reported in persons over 50 years [31]. In macaques, spine

density in the neocortex decreased significantly with ageing [32], [33] and was associated with a loss of synapses [34]. Overall dendritic spine changes with age have been well described elsewhere [34], [35]. These results reflect well the differences in grey matter shrinkage found between the various brain regions, as mentioned above. Myelinated nerve fibres from the white matter are also affected by normal ageing. While a part of them are lost, another part loses its myelin sheath which is incompletely remyelinated by oligodendrocytes, the number of which increases with ageing, negatively affecting the conduction velocity along nerve fibres [36], [37]. Thus, there is a constitutive myelination activity, potentially explaining the increase in the expression of genes involved in myelination function during ageing [9], [38], [39]. Paradoxically, the sheath thickness of some nerve fibres is continuously increasing because of this sustained activity [36], [40]. As these changes seem to occur quite early in life, some authors suggest that myelin is the most susceptible part of the brain to ageing [41]. On the other hand, glial cells' activity and number both increase with age [42]–[45] and most upregulated genes in the brain are of glial origin [46]. In the main, microglia activation is recognized as sustaining a pro-inflammatory environment [47], [48] which could increase neurons' susceptibility to neurodegeneration [49] and loss of synapses [50], [51]. Finally, neurogenesis is also impaired with ageing. While most neurons in the adult brain are produced during embryogenesis or very early in life, adult neurogenesis has been identified in the hippocampus, the sub-ventricular zone and in the olfactory bulb of the mammalian brain [52], [53]. Although data are still lacking, neurogenesis seems to decline with advancing age, with an already significant decline by middle age, particularly in the hippocampus [52]–[55]. However, the significance of this decline is not fully understood yet [52].

2.3. AD-related changes

Neurofibrillary tangles (NFT) and senile plaques (SP), the two main neuropathological lesions associated with the definitive diagnosis of AD, are frequently observed in the brains of elderly individuals with normal cognitive functions. This very common occurrence has led to the currently unresolved question as to what extent the presence of non-pathological, AD-related lesions should be considered as normal ageing (i.e. preclinical AD).

NFT are characterized by the intracellular accumulation of abnormally-hyperphosphorylated Tau proteins into filamentous inclusions known as paired helicoidal filaments [56]. Many studies have confirmed the consistency of their localization: the entorhinal cortex and the CA1 field of the hippocampus are the first brain regions where NFT occur, while only sparse lesions are present in the adjacent temporal neocortex or frontal neocortex (Figure 1C). NFT predominate in layer II, and to a lesser extent III and V, of the entorhinal cortex. This typical distribution of NFT is now widely recognized as the initial stages I and II (of VI) in the hierarchical and progressive spreading of neurofibrillary pathology described 30 years ago by Braak and Braak [57]. More recent neuropathological studies, focusing on subcortical and brainstem nuclei, have even showed that the first NFT may appear in teenagers in the locus coeruleus. Some authors, mostly from the US, consider the early and mid-stages of this neurofibrillary pathology to be a specific pathological process, independent of AD pathology, and potentially associated with cognitive decline. They coined the term “PART” (Primary Age-Related Tauopathy) to describe this neuropathological phenotype [58], but the concept has not attained a widespread, international consensus and remains controversial [59].

SP result from the extracellular aggregation of A β peptides [60]. Several A β peptides, of between 38 and 42 amino acids, derive from a larger transmembrane protein APP (amyloid precursor protein) after a complex cleavage process involving three main secretases (α , β , and γ). The microscopic aspect of amyloid deposits in brain tissue is heterogeneous. Classically, neuropathologists distinguish between diffuse amyloid deposits, characterized by their ill limited extent and their lack of affinity for “amyloid” specific stains such as Congo-Red, and dense amyloid deposits that are usually well defined and comprise a dense amyloid core surrounded by a corona of dystrophic neurites. Amyloid deposits associated with ageing are mostly diffuse (Fig. 1D). Their topographical extent usually includes the orbitofrontal, occipital and precuneus cortex, the hippocampus, and the basal ganglia. In other words, such amyloid deposits correspond to Thal phases 1 to 3 (of 5) [61].

Figure 2 summarises the estimated prevalence of amyloid deposits, hippocampal neurofibrillary pathology (Braak stages I and II), and extensive neocortical neurofibrillary pathology (Braak V and VI) according to the age of the subjects [62]. These data come from large autopsy cohorts, especially from Braak and Braak (more than 2660 brains grouped into age classes) [63]. Despite the fact that such post-mortem, epidemiological studies lack clinical information and are potentially biased owing to the possibility of unrecorded, underlying pathologies which can affect brain ageing, it is interesting to notice that the median age for the presence of hippocampal NFT is around 45 years of age. Almost all subjects aged over 80 years present hippocampal neurofibrillary pathology. The median age for cortical amyloid pathology is about 75, but the prevalence curve of amyloid deposits does not seem to reach 100%, even in centenarians. The prevalence of high Braak stages for neurofibrillary pathology is close to that of AD in elderly patients. Such data are important to keep in mind when interpreting biological and imaging biomarkers of AD in cohorts of elderly people.

2.4. Other neurodegenerative lesions in the ageing brain

Various other pathologies have been described in the ageing brain, among them argyrophilic grains (Fig. 1E), characterized by the synaptic accumulation of Tau protein isoforms with four microtubule-bonding domains, mostly in the pyramidal layer of the hippocampus. Grains are known to be age-related [64], [65] and were consistently observed in the brains of a group of 29 centenarians [66]. TDP-43 pathology has also been observed in almost 20% of aged controls [67]; once again, the hippocampus was the most vulnerable structure for TDP-43 accumulation.

2.5. Cerebrovascular changes

The microvascular system of the brain consists of pre-capillaries and capillaries, devoid of smooth muscle cells, forming a three-dimensional network within the brain parenchyma. This network is perfused by penetrating arterioles which represent the termini of brain vasculature. The absence of functional shunts between the penetrating arteries explains the vulnerability of the brain to ischaemia in case of thrombosis or global hypoperfusion. Normal ageing affects both the macro- and microvascular systems of the brain, resulting in altered cerebral blood flow in elderly people [68]. The arterioles supplying the deep white matter have the longest course through the brain and they often become tortuous with age: Hassler found that they were sparse in subjects under the age of 60, but common after the age of 70 [69]. Akima et al.

found them to appear in the 5th decade and to occur in all specimens above 80 years old [70]. Capillary loss in normal ageing was evaluated as between 15 and 50%, according to the cortical or subcortical region [71], [72]. The high frequency of leukoaraisosis in elderly people may be explained by these changes in brain vasculature.

3. Molecular ageing of the brain

3.1. Modifications in gene expression

One of the main hallmarks of ageing is the modification of genes' expression [73] and an increasing number of genes becomes upregulated or downregulated as we grow older. These changes in expression are mostly explained by epigenetic alterations which include several kinds of DNA and histone modifications that alter transcription [74]. The importance of these modifications led to the publication of a recent multi-omic atlas of the brain's frontal cortex during ageing providing data on DNA mutations, changes in RNA and miRNA expression, and in DNA methylation and Histone 3 Lysine 9 acetylation [75]. With ageing, DNA becomes globally hypomethylated but the hypermethylation of 353 CpG sites is one of the best markers of ageing and has even been proposed as an "epigenetic clock" [76]–[78]. While there is no significant change in the expression of most genes in the brain, more than 150 do undergo a significant modification of their expression with age with a high degree of conservation between cohorts [9], [79]. Contrary to most other tissues where genes' expression is mainly upregulated with ageing, changes in gene expression in the human brain are predominantly shifts towards downregulation [9]. Genes which are downregulated in the brain are associated with the functions of mitochondria, neural plasticity/synapses, inhibitory interneurons and the ubiquitin-proteasome system (UPS). On the contrary, genes associated with stress response, immune/inflammatory response, metal ion homeostasis, myelin-related functions and glia tend to be upregulated [9], [38]. These trends are well conserved between rhesus macaques and humans but discrepancies exist in rodents where most changes are characterized by an upregulation of genes' expression, notably of those participating in neuronal functions [9], [80]. Accordingly, a recent study identified that genes involved in immunity, and more precisely in the complement system, in synaptic transmission and in myelination were very good biomarkers of brain ageing. Genes involved in synaptic transmission were negatively correlated with the genes related to immunity while genes involved in myelination showed a positive correlation with immunity-related genes (Table 1) [39]. It is possible that the increased immune reactions with ageing are in fact drivers of the downregulation of the expression of genes involved in synaptic transmission [81]–[83]. This involvement of immunity in brain ageing is perfectly in line with the concept of inflammaging, defined as a chronic, sterile and low-grade inflammation which actively contributes to ageing and is considered a very good predictor of successful ageing [84]–[86].

Because of modulations in gene expression with ageing, a number of mRNAs and proteins essential to brain function are affected. The mRNA levels of brain-derived neurotrophic factor (BDNF) and its receptor tyrosine kinase B (trkB), key modulators of brain plasticity, seem to be affected by ageing in specific areas of the brain. While *BDNF* levels remained stable over time in the hippocampus, the expression of its receptor was significantly decreased with age [87]. More changes were found in the prefrontal cortex, notably in the Brodmann area 9, as both *BDNF* and *trkB* showed a decreased expression with ageing [46], [87], [88]. Interestingly,

β -amyloid peptides, which accumulate even during normal ageing [89], [90], were shown to impair BDNF signalling [91]. As a consequence of decreased BDNF or impaired signalling, the expression of many essential genes is compromised, mainly in gamma aminobutyric acid (GABA) neurons [92], which results notably in alterations in both inhibitory and excitatory synapses [93]. Other neuropeptides such as somatostatin, neuropeptide Y or cortistatin, which can be produced in subtypes of GABA interneurons and target dendrites of pyramidal dendrites, are also significantly reduced with ageing [79], [93]. Post-synaptic GABA receptors were also decreased in older subjects, further impairing the functioning of GABA neurons [93]. Such variations in expression or functionality are also found in other receptors such as nicotinic and muscarinic acetylcholine receptors [94], [95], metabotropic glutamate receptors [96], [97], N-methyl-D-aspartate (NMDA) receptors [98]–[100], serotonin receptors [101] or dopamine receptors [102].

3.2. Insulin/insulin-like growth factor 1 signalling

Insulin/insulin-like growth factor 1 (IGF-1) signalling (IIS) has also been implicated in brain ageing. This pathway is involved in protein synthesis, proliferation and cell survival, notably acting through the rapamycin (mTOR) pathway, and is highly conserved through evolution [103]–[105]. Its inhibition, through various means, importantly leads to increased lifespan in multiple species [106]–[110]. Interestingly, and paradoxically, the IIS pathway has been shown to be neuroprotective and IGF-1 acts as a neurotrophic agent [111], [112] but its repression can reduce the consequences of AD in murine models [111], [113]. It has been suggested that IGF-1 plays an essential role in cell proliferation during recovery after acute events such as strokes, while its inhibition of stress-resistance or autophagy becomes detrimental in situations like ageing where cellular debris and damage may accumulate [114]. Interestingly, growth hormone (GH), produced by the pituitary, is a major regulator of IGF-1 secretion and limitation of pituitary development significantly increased lifespan in murine models [115]–[117]. This suggests an interplay between these components.

3.3. Post-translational protein modifications

In addition to the changes described above, major protein modifications occur in the brain during normal ageing and participate in the accumulation of cellular debris. The ubiquitination of proteins is a process required for degradation of damaged, misfolded proteins by the UPS; however undegraded, ubiquitinated proteins are found to accumulate in the brain with ageing [118]–[120], suggesting an impairment of the UPS and resulting in the accumulation of these detrimental proteins [121]–[123]. In addition, non-enzymatic modifications such as oxidation, notably produced when proteins react with reactive oxygen species (ROS), are also increased during normal brain ageing [124], [125]. Iron accumulation with ageing is also an important contributor to oxidation [31], [126]. This leads to a change in proteins' function and modified proteins can accumulate with other intracellular molecular debris to form lipofuscin, which accumulates in brains over time [127], [128]. The number of corpora amylacea (spherical polyglucosan bodies which may contain cell debris) also increases with age [31], [129]. Products of glycation, another non-enzymatic reaction between nucleophiles and carbonyl compounds and favoured by oxidation, also accumulate in ageing brains [130]. These modifications all produce significant changes in proteins' structure, leading to their degradation or, on the contrary, to their aggregation. Cross-links can occur,

forming uncontrolled complex structures with important consequences on protein function and leading, for example, to increased vascular stiffness [131]–[134]. In addition, advanced glycation end-products (AGEs) can interact with the receptor for AGEs (RAGE), whose expression in the brain is increased with age, producing a vicious circle of signalling and activation that contributes to chronic, low-grade inflammation [135], [136]. Amyloidosis, an aggregation of insoluble and misfolded fibrils more widely studied in the context of AD which can be promoted by glycation [137], is also increased in brains of elderly people without cognitive impairment [138], [139]. Overall, such loss of proteostasis can notably promote the unfolded protein response, lead to apoptosis or induce senescence, all of which are particularly detrimental in a tissue in which cell renewal is limited [140]–[142].

3.4. Mitochondrial dysfunction

Together with muscles, the brain has a higher metabolic activity than all other organs, hence the brain may be more susceptible to mitochondrial dysfunction, a key hallmark of ageing [73], [143]. With time, mitochondria accumulate mutations which are associated with homoplasmy and, as mentioned earlier, a diminished expression of mitochondrial proteins. As a consequence of such modifications, electron leakage occurs throughout the respiratory chain producing ROS and, in turn, increasing cell and mitochondrial damage [144]–[148]. Disruption of the electron transport chain also results in mitochondria with depolarized membranes [149]. Of note, since brain metabolism requires high oxygen consumption, the probability of producing ROS may be further increased. It is also important to note that while large amounts of ROS are detrimental, lower levels can stimulate a pro-survival response [73], [150], [151]. Decline in mitochondrial function provokes a decline in nicotinamide adenine dinucleotide (NAD⁺) levels, notably affecting the activity the NAD⁺-dependent sirtuins [152], [153]. This dysfunction may also lead to increased inflammation, as well as altered apoptosis and disrupted crosstalk among organelles [145], [154], [155]. The importance of mitochondrial dysfunction in ageing is underlined by an innovative study showing that mitochondrial removal from senescent cells diminished pro-ageing features of senescence [156]. More specific to the brain, projection neurons rely upon energy production by mitochondria to support ion fluxes and axonal transport, making them particularly vulnerable to mitochondrial dysfunction [157], [158]. With decreased energy production by mitochondria, a reduction in metabolic activities has been reported in the subiculum and dentate gyrus [159], a finding which was confirmed in another study in rats where the activities of both mitochondrial complexes and nitric oxide synthase were significantly reduced in the hippocampus and, to a lesser extent, in the cortex [160].

3.5. Autophagy

Autophagy is a process which permits cells to produce nutrients for themselves when extracellular nutrient concentrations are low, or under conditions of stress, and involves degrading cell components (mainly damaged cell debris) in autolysosomes formed by the fusion of an autophagosome with a lysosome. The mTOR pathway is an inhibitor of autophagy and, as mentioned earlier, is stimulated by IGF-1. Thus, sustained IGF-1 and mTOR signalling may prevent the autophagic recycling of damaged proteins and facilitate their aggregation and subsequent detrimental consequences. A similar process, mitophagy, exists for the degradation of damaged mitochondria. Impairment of both of these processes as

a result of ageing accelerates the deleterious effects of cytotoxic cellular and organelle-derived components. Hence, suppression of autophagy has been identified as a cause of neurodegeneration [161]–[163] while its enhancement ameliorates cognitive functions [164]–[166]. In murine hippocampus, autophagic activity is decreased with ageing but this observation was not explained by an overactivated mTOR signalling, therefore other parameters must be responsible for this decline [167]. The decrease in *BECN1* expression in older human brains, a key regulator of autophagy, [168] suggests that autophagy may also decline with age in humans, but as extensively reviewed elsewhere, there is currently insufficient data on autophagy evolution during normal human brain ageing to definitively conclude on this matter [169].

3.6. Calcium conductance

Correct Ca^{2+} conductance and homeostasis are essential for signal propagation in the brain and their alteration might result in a deterioration of inter-neuronal communication. These changes in Ca^{2+} signalling in the ageing brain have been extensively reviewed elsewhere [170]–[172]. Mainly, Ca^{2+} conductance is increased in aged neurons as shown in the hippocampus where there is an increase in L-type, voltage-dependent Ca^{2+} channels' density and activity in pyramidal cells [173], [174]. The release of Ca^{2+} from intracellular organelles is also altered by ageing as the endoplasmic reticulum calcium releasing channels, the inositol trisphosphate receptor (IP_3R) and ryanodine receptor (RyR) all show an increased activity over time, partly mediated by ROS oxidation [175], [176]. On the other hand, Ca^{2+} buffering is impaired as the activities of both the sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) and the plasma membrane Ca^{2+} ATPase (PMCA) pumps are decreased, potentially because of a reduction in available ATP and oxidation as consequences of mitochondrial dysfunction [176]–[178]. Diminished mitochondrial Ca^{2+} buffering capability has also been reported [179]. In addition, calcium-binding proteins such as calbindin 1 are overwhelmingly downregulated with age in the prefrontal cortex [46], [180], further impairing Ca^{2+} signalling.

4. Conclusion

All the hallmarks of ageing are observable in the ageing brain and its structures [143]. Most of the current knowledge of the ageing brain derives from studies of neurodegenerative disorders. It is interesting to recognize that changes like Tau, phosphoTau and amyloid peptide accumulation can begin in early life as a result of physiological ageing and are present in subclinical cases while also being used as early-stage markers of neurodegenerative diseases in progression. It will be important to increase research of normal ageing to better understand pathological ageing of the brain. Identification of new biomarkers, and progress in the field of functional neuroimaging, will help to better distinguish normal from pathological brain ageing and contribute to diagnosing the latter as early as possible.

5. Disclosure of interest

The authors declare no conflict of interest.

6. Acknowledgements

We are grateful to Mike Howsam for his contribution of editorial assistance and English proofreading.

7. Bibliography

- [1] J. J. Iliff *et al.*, 'A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β ', *Sci Transl Med*, vol. 4, no. 147, p. 147ra111, Aug. 2012, doi: 10.1126/scitranslmed.3003748.
- [2] A. K. Miller and J. A. Corsellis, 'Evidence for a secular increase in human brain weight during the past century', *Ann. Hum. Biol.*, vol. 4, no. 3, pp. 253–257, May 1977.
- [3] A. S. Dekaban, 'Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights', *Ann. Neurol.*, vol. 4, no. 4, pp. 345–356, Oct. 1978, doi: 10.1002/ana.410040410.
- [4] K. C. Ho, U. Roessmann, J. V. Straumfjord, and G. Monroe, 'Analysis of brain weight. I. Adult brain weight in relation to sex, race, and age', *Arch. Pathol. Lab. Med.*, vol. 104, no. 12, pp. 635–639, Dec. 1980.
- [5] L. Svennerholm, K. Boström, and B. Jungbjer, 'Changes in weight and compositions of major membrane components of human brain during the span of adult human life of Swedes', *Acta Neuropathol.*, vol. 94, no. 4, pp. 345–352, Oct. 1997, doi: 10.1007/s004010050717.
- [6] J. M. Anderson, B. M. Hubbard, G. R. Coghill, and W. Slidders, 'The effect of advanced old age on the neurone content of the cerebral cortex. Observations with an automatic image analyser point counting method', *J. Neurol. Sci.*, vol. 58, no. 2, pp. 235–246, Feb. 1983, doi: 10.1016/0022-510x(83)90220-4.
- [7] S. M. Resnick, D. L. Pham, M. A. Kraut, A. B. Zonderman, and C. Davatzikos, 'Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain', *J. Neurosci.*, vol. 23, no. 8, pp. 3295–3301, Apr. 2003.
- [8] M. J. West, 'Stereological methods for estimating the total number of neurons and synapses: issues of precision and bias', *Trends Neurosci.*, vol. 22, no. 2, pp. 51–61, Feb. 1999.
- [9] N. A. Bishop, T. Lu, and B. A. Yankner, 'Neural mechanisms of ageing and cognitive decline', *Nature*, vol. 464, no. 7288, pp. 529–535, Mar. 2010, doi: 10.1038/nature08983.
- [10] H. Haug, S. Kühl, E. Mecke, N. L. Sass, and K. Wasner, 'The significance of morphometric procedures in the investigation of age changes in cytoarchitectonic structures of human brain', *J Hirnforsch*, vol. 25, no. 4, pp. 353–374, 1984.
- [11] T. Gómez-Isla *et al.*, 'Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease', *Ann. Neurol.*, vol. 41, no. 1, pp. 17–24, Jan. 1997, doi: 10.1002/ana.410410106.
- [12] B. Pakkenberg and H. J. Gundersen, 'Neocortical neuron number in humans: effect of sex and age', *J. Comp. Neurol.*, vol. 384, no. 2, pp. 312–320, Jul. 1997.
- [13] M. J. West, P. D. Coleman, D. G. Flood, and J. C. Troncoso, 'Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease', *Lancet*, vol. 344, no. 8925, pp. 769–772, Sep. 1994, doi: 10.1016/s0140-6736(94)92338-8.
- [14] D. M. A. Mann, 'The locus coeruleus and its possible role in ageing and degenerative disease of the human central nervous system', *Mechanisms of Ageing and Development*, vol. 23, no. 1, pp. 73–94, Sep. 1983, doi: 10.1016/0047-6374(83)90100-8.
- [15] C. D. Good, I. S. Johnsrude, J. Ashburner, R. N. A. Henson, K. J. Friston, and R. S. J. Frackowiak, 'A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains', *NeuroImage*, vol. 14, no. 1, pp. 21–36, Jul. 2001, doi: 10.1006/nimg.2001.0786.
- [16] S. M. Resnick, D. L. Pham, M. A. Kraut, A. B. Zonderman, and C. Davatzikos, 'Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain', *J. Neurosci.*, vol. 23, no. 8, pp. 3295–3301, Apr. 2003.

- [17] D. L. Dickstein, D. Kabaso, A. B. Rocher, J. I. Luebke, S. L. Wearne, and P. R. Hof, 'Changes in the structural complexity of the aged brain', *Aging Cell*, vol. 6, no. 3, pp. 275–284, Jun. 2007, doi: 10.1111/j.1474-9726.2007.00289.x.
- [18] L. Marstaller, M. Williams, A. Rich, G. Savage, and H. Burianová, 'Aging and large-scale functional networks: white matter integrity, gray matter volume, and functional connectivity in the resting state', *Neuroscience*, vol. 290, pp. 369–378, Apr. 2015, doi: 10.1016/j.neuroscience.2015.01.049.
- [19] I. J. Bennett and D. J. Madden, 'Disconnected aging: cerebral white matter integrity and age-related differences in cognition', *Neuroscience*, vol. 276, pp. 187–205, Sep. 2014, doi: 10.1016/j.neuroscience.2013.11.026.
- [20] B. P. Drayer, 'Imaging of the aging brain. Part I. Normal findings', *Radiology*, vol. 166, no. 3, pp. 785–796, Mar. 1988, doi: 10.1148/radiology.166.3.3277247.
- [21] T. Hedden and J. D. E. Gabrieli, 'Insights into the ageing mind: a view from cognitive neuroscience', *Nature Reviews Neuroscience*, vol. 5, no. 2, pp. 87–96, Feb. 2004, doi: 10.1038/nrn1323.
- [22] D. G. Flood, S. J. Buell, G. J. Horwitz, and P. D. Coleman, 'Dendritic extent in human dentate gyrus granule cells in normal aging and senile dementia', *Brain Res.*, vol. 402, no. 2, pp. 205–216, Feb. 1987, doi: 10.1016/0006-8993(87)90027-8.
- [23] S. D. Hanks and D. G. Flood, 'Region-specific stability of dendritic extent in normal human aging and regression in Alzheimer's disease. I. CA1 of hippocampus', *Brain Res.*, vol. 540, no. 1–2, pp. 63–82, Feb. 1991, doi: 10.1016/0006-8993(91)90493-f.
- [24] D. G. Flood, M. Guarnaccia, and P. D. Coleman, 'Dendritic extent in human CA2-3 hippocampal pyramidal neurons in normal aging and senile dementia', *Brain Res.*, vol. 409, no. 1, pp. 88–96, Apr. 1987, doi: 10.1016/0006-8993(87)90744-x.
- [25] D. G. Flood, 'Region-specific stability of dendritic extent in normal human aging and regression in Alzheimer's disease. II. Subiculum', *Brain Res.*, vol. 540, no. 1–2, pp. 83–95, Feb. 1991, doi: 10.1016/0006-8993(91)90494-g.
- [26] R. S. Williams and S. Matthyse, 'Age-related changes in Down syndrome brain and the cellular pathology of Alzheimer disease', *Prog. Brain Res.*, vol. 70, pp. 49–67, 1986, doi: 10.1016/s0079-6123(08)64297-1.
- [27] C. A. Curcio and J. W. Hinds, 'Stability of synaptic density and spine volume in dentate gyrus of aged rats', *Neurobiol. Aging*, vol. 4, no. 1, pp. 77–87, 1983, doi: 10.1016/0197-4580(83)90058-1.
- [28] J. D. Grill and D. R. Riddle, 'Age-related and laminar-specific dendritic changes in the medial frontal cortex of the rat', *Brain Res.*, vol. 937, no. 1–2, pp. 8–21, May 2002, doi: 10.1016/s0006-8993(02)02457-5.
- [29] J. A. Markham and J. M. Juraska, 'Aging and sex influence the anatomy of the rat anterior cingulate cortex', *Neurobiol. Aging*, vol. 23, no. 4, pp. 579–588, Aug. 2002, doi: 10.1016/s0197-4580(02)00004-0.
- [30] J. M. de Brabander, R. J. Kramers, and H. B. Uylings, 'Layer-specific dendritic regression of pyramidal cells with ageing in the human prefrontal cortex', *Eur. J. Neurosci.*, vol. 10, no. 4, pp. 1261–1269, Apr. 1998, doi: 10.1046/j.1460-9568.1998.00137.x.
- [31] B. Jacobs, L. Driscoll, and M. Schall, 'Life-span dendritic and spine changes in areas 10 and 18 of human cortex: a quantitative Golgi study', *J. Comp. Neurol.*, vol. 386, no. 4, pp. 661–680, Oct. 1997.
- [32] D. Kabaso, P. J. Coskren, B. I. Henry, P. R. Hof, and S. L. Wearne, 'The electrotonic structure of pyramidal neurons contributing to prefrontal cortical circuits in macaque monkeys is significantly altered in aging', *Cereb. Cortex*, vol. 19, no. 10, pp. 2248–2268, Oct. 2009, doi: 10.1093/cercor/bhn242.

- [33] H. Duan, S. L. Wearne, A. B. Rocher, A. Macedo, J. H. Morrison, and P. R. Hof, 'Age-related dendritic and spine changes in corticocortically projecting neurons in macaque monkeys', *Cereb. Cortex*, vol. 13, no. 9, pp. 950–961, Sep. 2003, doi: 10.1093/cercor/13.9.950.
- [34] J. H. Morrison and M. G. Baxter, 'The Aging Cortical Synapse: Hallmarks and Implications for Cognitive Decline', *Nat Rev Neurosci*, vol. 13, no. 4, pp. 240–250, Mar. 2012, doi: 10.1038/nrn3200.
- [35] D. L. Dickstein, C. M. Weaver, J. I. Luebke, and P. R. Hof, 'Dendritic spine changes associated with normal aging', *Neuroscience*, vol. 251, pp. 21–32, Oct. 2013, doi: 10.1016/j.neuroscience.2012.09.077.
- [36] A. Peters, 'The Effects of Normal Aging on Myelinated Nerve Fibers in Monkey Central Nervous System', *Front Neuroanat*, vol. 3, Jul. 2009, doi: 10.3389/neuro.05.011.2009.
- [37] A. Peters, 'The effects of normal aging on myelin and nerve fibers: a review', *J. Neurocytol.*, vol. 31, no. 8–9, pp. 581–593, Nov. 2002, doi: 10.1023/a:1025731309829.
- [38] A. Tripathi, 'New cellular and molecular approaches to ageing brain', *Ann Neurosci*, vol. 19, no. 4, pp. 177–182, Oct. 2012, doi: 10.5214/ans.0972.7531.190410.
- [39] S.-H. Bae, H. W. Kim, S. Shin, J. Kim, Y.-H. Jeong, and J. Moon, 'Decipher reliable biomarkers of brain aging by integrating literature-based evidence with interactome data', *Experimental & Molecular Medicine*, vol. 50, no. 4, pp. 1–15, Apr. 2018, doi: 10.1038/s12276-018-0057-6.
- [40] K. E. Stahon, C. Bastian, S. Griffith, G. J. Kidd, S. Brunet, and S. Baltan, 'Age-Related Changes in Axonal and Mitochondrial Ultrastructure and Function in White Matter', *J. Neurosci.*, vol. 36, no. 39, pp. 9990–10001, Sep. 2016, doi: 10.1523/JNEUROSCI.1316-16.2016.
- [41] F. Xie, P. Liang, H. Fu, J.-C. Zhang, and J. Chen, 'Effects of normal aging on myelin sheath ultrastructures in the somatic sensorimotor system of rats', *Molecular Medicine Reports*, vol. 10, no. 1, pp. 459–466, Jul. 2014, doi: 10.3892/mmr.2014.2228.
- [42] M. M. Esiri, 'Ageing and the brain', *J. Pathol.*, vol. 211, no. 2, pp. 181–187, Jan. 2007, doi: 10.1002/path.2089.
- [43] J. R. Conde and W. J. Streit, 'Microglia in the aging brain', *J. Neuropathol. Exp. Neurol.*, vol. 65, no. 3, pp. 199–203, Mar. 2006, doi: 10.1097/01.jnen.0000202887.22082.63.
- [44] J. W. Unger, 'Glial reaction in aging and Alzheimer's disease', *Microsc. Res. Tech.*, vol. 43, no. 1, pp. 24–28, Oct. 1998, doi: 10.1002/(SICI)1097-0029(19981001)43:1<24::AID-JEMT4>3.0.CO;2-P.
- [45] C. E. Finch, 'Neurons, glia, and plasticity in normal brain aging', *Neurobiol. Aging*, vol. 24 Suppl 1, pp. S123-127; discussion S131, Jun. 2003, doi: 10.1016/s0197-4580(03)00051-4.
- [46] L. Erraji-Benchekroun *et al.*, 'Molecular aging in human prefrontal cortex is selective and continuous throughout adult life', *Biol. Psychiatry*, vol. 57, no. 5, pp. 549–558, Mar. 2005, doi: 10.1016/j.biopsych.2004.10.034.
- [47] D. H. Cribbs *et al.*, 'Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study', *J Neuroinflammation*, vol. 9, p. 179, Jul. 2012, doi: 10.1186/1742-2094-9-179.
- [48] D. M. Norden and J. P. Godbout, 'Review: microglia of the aged brain: primed to be activated and resistant to regulation', *Neuropathol. Appl. Neurobiol.*, vol. 39, no. 1, pp. 19–34, Feb. 2013, doi: 10.1111/j.1365-2990.2012.01306.x.

- [49] M. Colonna and O. Butovsky, 'Microglia Function in the Central Nervous System During Health and Neurodegeneration', *Annu. Rev. Immunol.*, vol. 35, pp. 441–468, 2017, doi: 10.1146/annurev-immunol-051116-052358.
- [50] S. Hao, A. Dey, X. Yu, and A. M. Stranahan, 'Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity', *Brain Behav. Immun.*, vol. 51, pp. 230–239, Jan. 2016, doi: 10.1016/j.bbi.2015.08.023.
- [51] A. M. Stranahan *et al.*, 'Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats', *Hippocampus*, vol. 18, no. 11, pp. 1085–1088, 2008, doi: 10.1002/hipo.20470.
- [52] P. Baptista and J. P. Andrade, 'Adult Hippocampal Neurogenesis: Regulation and Possible Functional and Clinical Correlates', *Front. Neuroanat.*, vol. 12, 2018, doi: 10.3389/fnana.2018.00044.
- [53] D. R. Riddle and R. J. Lichtenwalner, 'Neurogenesis in the Adult and Aging Brain', in *Brain Aging: Models, Methods, and Mechanisms*, D. R. Riddle, Ed. Boca Raton (FL): CRC Press/Taylor & Francis, 2007.
- [54] O. Lazarov, M. P. Mattson, D. A. Peterson, S. W. Pimplikar, and H. van Praag, 'When neurogenesis encounters aging and disease', *Trends Neurosci.*, vol. 33, no. 12, pp. 569–579, Dec. 2010, doi: 10.1016/j.tins.2010.09.003.
- [55] V. Galvan and K. Jin, 'Neurogenesis in the aging brain', *Clin Interv Aging*, vol. 2, no. 4, pp. 605–610, Dec. 2007.
- [56] I. Grundke-Iqbal, K. Iqbal, M. Quinlan, Y. C. Tung, M. S. Zaidi, and H. M. Wisniewski, 'Microtubule-associated protein tau. A component of Alzheimer paired helical filaments', *J. Biol. Chem.*, vol. 261, no. 13, pp. 6084–6089, May 1986.
- [57] H. Braak and E. Braak, 'Neuropathological staging of Alzheimer-related changes', *Acta Neuropathol.*, vol. 82, no. 4, pp. 239–259, 1991, doi: 10.1007/bf00308809.
- [58] J. F. Cray *et al.*, 'Primary age-related tauopathy (PART): a common pathology associated with human aging', *Acta Neuropathol.*, vol. 128, no. 6, pp. 755–766, Dec. 2014, doi: 10.1007/s00401-014-1349-0.
- [59] C. Duyckaerts *et al.*, 'PART is part of Alzheimer disease', *Acta Neuropathol.*, vol. 129, no. 5, pp. 749–756, May 2015, doi: 10.1007/s00401-015-1390-7.
- [60] G. G. Glenner and C. W. Wong, 'Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein', *Biochem. Biophys. Res. Commun.*, vol. 120, no. 3, pp. 885–890, May 1984, doi: 10.1016/s0006-291x(84)80190-4.
- [61] D. R. Thal, U. Rüb, M. Orantes, and H. Braak, 'Phases of A beta-deposition in the human brain and its relevance for the development of AD', *Neurology*, vol. 58, no. 12, pp. 1791–1800, Jun. 2002, doi: 10.1212/wnl.58.12.1791.
- [62] C. Duyckaerts and J. J. Hauw, 'Prevalence, incidence and duration of Braak's stages in the general population: can we know?', *Neurobiol. Aging*, vol. 18, no. 4, pp. 362–369; discussion 389–392, Aug. 1997, doi: 10.1016/s0197-4580(97)00047-x.
- [63] H. Braak and E. Braak, 'Diagnostic criteria for neuropathologic assessment of Alzheimer's disease', *Neurobiol. Aging*, vol. 18, no. 4 Suppl, pp. S85–88, Aug. 1997, doi: 10.1016/s0197-4580(97)00062-6.
- [64] Z.-T. Ding *et al.*, 'Argyrophilic grain disease: frequency and neuropathology in centenarians', *Acta Neuropathol.*, vol. 111, no. 4, pp. 320–328, Apr. 2006, doi: 10.1007/s00401-006-0043-2.
- [65] K. A. Josephs *et al.*, 'Argyrophilic grains: a distinct disease or an additive pathology?', *Neurobiol. Aging*, vol. 29, no. 4, pp. 566–573, Apr. 2008, doi: 10.1016/j.neurobiolaging.2006.10.032.

- [66] C.-T. Pham *et al.*, 'Tau-positive grains are constant in centenarians' hippocampus', *Neurobiol. Aging*, vol. 32, no. 7, pp. 1296–1303, Jul. 2011, doi: 10.1016/j.neurobiolaging.2009.07.009.
- [67] K. E. McAleese, L. Walker, D. Erskine, A. J. Thomas, I. G. McKeith, and J. Attems, 'TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing', *Brain Pathol.*, vol. 27, no. 4, pp. 472–479, 2017, doi: 10.1111/bpa.12424.
- [68] W. R. Brown and C. R. Thore, 'Review: cerebral microvascular pathology in ageing and neurodegeneration', *Neuropathol. Appl. Neurobiol.*, vol. 37, no. 1, pp. 56–74, Feb. 2011, doi: 10.1111/j.1365-2990.2010.01139.x.
- [69] O. Hassler, 'Arterial deformities in senile brains. The occurrence of the deformities in a large autopsy series and some aspects of their functional significance', *Acta Neuropathol.*, vol. 8, no. 3, pp. 219–229, May 1967, doi: 10.1007/bf00688824.
- [70] M. Akima, H. Nonaka, M. Kagesawa, and K. Tanaka, 'A study on the microvasculature of the cerebral cortex. Fundamental architecture and its senile change in the frontal cortex', *Lab. Invest.*, vol. 55, no. 4, pp. 482–489, Oct. 1986.
- [71] W. B. Abernethy, M. A. Bell, M. Morris, and D. M. Moody, 'Microvascular density of the human paraventricular nucleus decreases with aging but not hypertension', *Exp. Neurol.*, vol. 121, no. 2, pp. 270–274, Jun. 1993, doi: 10.1006/exnr.1993.1095.
- [72] L. Buée *et al.*, 'Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders', *Acta Neuropathol.*, vol. 87, no. 5, pp. 469–480, 1994, doi: 10.1007/bf00294173.
- [73] C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer, 'The hallmarks of aging', *Cell*, vol. 153, no. 6, pp. 1194–1217, Jun. 2013, doi: 10.1016/j.cell.2013.05.039.
- [74] D. E. Handy, R. Castro, and J. Loscalzo, 'Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease', *Circulation*, vol. 123, no. 19, pp. 2145–2156, May 2011, doi: 10.1161/CIRCULATIONAHA.110.956839.
- [75] P. L. De Jager *et al.*, 'A multi-omic atlas of the human frontal cortex for aging and Alzheimer's disease research', *Sci Data*, vol. 5, Aug. 2018, doi: 10.1038/sdata.2018.142.
- [76] S. Horvath, 'DNA methylation age of human tissues and cell types', *Genome Biology*, vol. 14, no. 10, p. 3156, Oct. 2013, doi: 10.1186/gb-2013-14-10-r115.
- [77] S. Horvath and K. Raj, 'DNA methylation-based biomarkers and the epigenetic clock theory of ageing', *Nature Reviews Genetics*, vol. 19, no. 6, p. 371, Jun. 2018, doi: 10.1038/s41576-018-0004-3.
- [78] D. G. Hernandez *et al.*, 'Distinct DNA methylation changes highly correlated with chronological age in the human brain', *Hum Mol Genet.*, vol. 20, no. 6, pp. 1164–1172, Mar. 2011, doi: 10.1093/hmg/ddq561.
- [79] E. Sibille, 'Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders', *Dialogues Clin Neurosci*, vol. 15, no. 1, pp. 53–65, Mar. 2013.
- [80] P. M. Loerch *et al.*, 'Evolution of the aging brain transcriptome and synaptic regulation', *PLoS ONE*, vol. 3, no. 10, p. e3329, Oct. 2008, doi: 10.1371/journal.pone.0003329.
- [81] N. C. Berchtold, P. D. Coleman, D. H. Cribbs, J. Rogers, D. L. Gillen, and C. W. Cotman, 'Synaptic genes are extensively downregulated across multiple brain regions in normal human aging and Alzheimer's disease', *Neurobiol. Aging*, vol. 34, no. 6, pp. 1653–1661, Jun. 2013, doi: 10.1016/j.neurobiolaging.2012.11.024.
- [82] S. Hong *et al.*, 'Complement and microglia mediate early synapse loss in Alzheimer mouse models', *Science*, vol. 352, no. 6286, pp. 712–716, May 2016, doi: 10.1126/science.aad8373.

- [83] T. Lu *et al.*, 'Gene regulation and DNA damage in the ageing human brain', *Nature*, vol. 429, no. 6994, pp. 883–891, Jun. 2004, doi: 10.1038/nature02661.
- [84] C. Franceschi *et al.*, 'Inflamm-aging. An evolutionary perspective on immunosenescence', *Ann. N. Y. Acad. Sci.*, vol. 908, pp. 244–254, Jun. 2000.
- [85] B. K. Kennedy *et al.*, 'Aging: a common driver of chronic diseases and a target for novel interventions', *Cell*, vol. 159, no. 4, pp. 709–713, Nov. 2014, doi: 10.1016/j.cell.2014.10.039.
- [86] Y. Arai *et al.*, 'Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians', *EBioMedicine*, vol. 2, no. 10, pp. 1549–1558, Oct. 2015, doi: 10.1016/j.ebiom.2015.07.029.
- [87] M. J. Webster, M. M. Herman, J. E. Kleinman, and C. Shannon Weickert, 'BDNF and *trkB* mRNA expression in the hippocampus and temporal cortex during the human lifespan', *Gene Expr. Patterns*, vol. 6, no. 8, pp. 941–951, Oct. 2006, doi: 10.1016/j.modgep.2006.03.009.
- [88] L. Tapia-Arancibia, E. Aliaga, M. Silhol, and S. Arancibia, 'New insights into brain BDNF function in normal aging and Alzheimer disease', *Brain Research Reviews*, vol. 59, no. 1, pp. 201–220, Nov. 2008, doi: 10.1016/j.brainresrev.2008.07.007.
- [89] A. Piccini *et al.*, 'beta-amyloid is different in normal aging and in Alzheimer disease', *J. Biol. Chem.*, vol. 280, no. 40, pp. 34186–34192, Oct. 2005, doi: 10.1074/jbc.M501694200.
- [90] K. M. Rodrigue *et al.*, 'β-Amyloid burden in healthy aging', *Neurology*, vol. 78, no. 6, pp. 387–395, Feb. 2012, doi: 10.1212/WNL.0b013e318245d295.
- [91] L. Tong, R. Balazs, P. L. Thornton, and C. W. Cotman, 'Beta-amyloid peptide at sublethal concentrations downregulates brain-derived neurotrophic factor functions in cultured cortical neurons', *J. Neurosci.*, vol. 24, no. 30, pp. 6799–6809, Jul. 2004, doi: 10.1523/JNEUROSCI.5463-03.2004.
- [92] C. Glorioso *et al.*, 'Specificity and timing of neocortical transcriptome changes in response to BDNF gene ablation during embryogenesis or adulthood', *Molecular Psychiatry*, vol. 11, no. 7, pp. 633–648, Jul. 2006, doi: 10.1038/sj.mp.4001835.
- [93] H. Oh, D. A. Lewis, and E. Sibille, 'The Role of BDNF in Age-Dependent Changes of Excitatory and Inhibitory Synaptic Markers in the Human Prefrontal Cortex', *Neuropsychopharmacology*, vol. 41, no. 13, pp. 3080–3091, Dec. 2016, doi: 10.1038/npp.2016.126.
- [94] Y. N. Utkin, 'Aging Affects Nicotinic Acetylcholine Receptors in Brain', *Cent Nerv Syst Agents Med Chem*, vol. 19, no. 2, pp. 119–124, 2019, doi: 10.2174/1871524919666190320102834.
- [95] R. Schliebs and T. Arendt, 'The cholinergic system in aging and neuronal degeneration', *Behav. Brain Res.*, vol. 221, no. 2, pp. 555–563, Aug. 2011, doi: 10.1016/j.bbr.2010.11.058.
- [96] E. Griego and E. J. Galván, 'Metabotropic Glutamate Receptors at the Aged Mossy Fiber – CA3 Synapse of the Hippocampus', *Neuroscience*, Jan. 2020, doi: 10.1016/j.neuroscience.2019.12.016.
- [97] C. M. Hernandez, J. A. McQuail, M. R. Schwabe, S. N. Burke, B. Setlow, and J. L. Bizon, 'Age-Related Declines in Prefrontal Cortical Expression of Metabotropic Glutamate Receptors that Support Working Memory', *eNeuro*, vol. 5, no. 3, Jun. 2018, doi: 10.1523/ENEURO.0164-18.2018.
- [98] X. Zhao *et al.*, 'The Effects of Aging on NMDA Receptor Subunits in the Synaptic Membrane and Relationships to Long-term Spatial Memory', *Neuroscience*, vol. 162, no. 4, pp. 933–945, Sep. 2009, doi: 10.1016/j.neuroscience.2009.05.018.

- [99] W. E. Müller, S. Stoll, K. Scheuer, and A. Meichelböck, 'The function of the NMDA-receptor during normal brain aging', *J. Neural Transm. Suppl.*, vol. 44, pp. 145–158, 1994, doi: 10.1007/978-3-7091-9350-1_11.
- [100] A. Kumar and T. C. Foster, 'Alteration in NMDA receptor mediated glutamatergic neurotransmission in the hippocampus during senescence', *Neurochem Res*, vol. 44, no. 1, pp. 38–48, Jan. 2019, doi: 10.1007/s11064-018-2634-4.
- [101] S. Banerjee and M. K. Poddar, 'Aging-induced changes in brain regional serotonin receptor binding: Effect of Carnosine', *Neuroscience*, vol. 319, pp. 79–91, Apr. 2016, doi: 10.1016/j.neuroscience.2016.01.032.
- [102] T. M. Karrer, A. K. Josef, R. Mata, E. D. Morris, and G. R. Samanez-Larkin, 'Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis', *Neurobiology of Aging*, vol. 57, pp. 36–46, Sep. 2017, doi: 10.1016/j.neurobiolaging.2017.05.006.
- [103] C. O'Neill, A. P. Kiely, M. F. Coakley, S. Manning, and C. M. Long-Smith, 'Insulin and IGF-1 signalling: longevity, protein homeostasis and Alzheimer's disease', *Biochem. Soc. Trans.*, vol. 40, no. 4, pp. 721–727, Aug. 2012, doi: 10.1042/BST20120080.
- [104] A. H. Khan, Z. Zou, Y. Xiang, S. Chen, and X.-L. Tian, 'Conserved signaling pathways genetically associated with longevity across the species', *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1865, no. 7, pp. 1745–1755, Jul. 2019, doi: 10.1016/j.bbadis.2018.09.001.
- [105] G. Vitale, G. Pellegrino, M. Vallery, and L. J. Hofland, 'ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective', *Front. Endocrinol.*, vol. 10, 2019, doi: 10.3389/fendo.2019.00027.
- [106] C. Kenyon, J. Chang, E. Gensch, A. Rudner, and R. Tabtiang, 'A *C. elegans* mutant that lives twice as long as wild type', *Nature*, vol. 366, no. 6454, pp. 461–464, Dec. 1993, doi: 10.1038/366461a0.
- [107] A. Ortega-Molina *et al.*, 'Pten positively regulates brown adipose function, energy expenditure, and longevity', *Cell Metab.*, vol. 15, no. 3, pp. 382–394, Mar. 2012, doi: 10.1016/j.cmet.2012.02.001.
- [108] M. Briga and S. Verhulst, 'What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments?', *Exp. Gerontol.*, vol. 71, pp. 21–26, Nov. 2015, doi: 10.1016/j.exger.2015.09.002.
- [109] N. M. Ashpole *et al.*, 'IGF-1 has sexually dimorphic, pleiotropic, and time-dependent effects on healthspan, pathology, and lifespan', *Geroscience*, vol. 39, no. 2, pp. 129–145, 2017, doi: 10.1007/s11357-017-9971-0.
- [110] S. N. Austad and J. M. Hoffman, 'Is antagonistic pleiotropy ubiquitous in aging biology?', *Evol Med Public Health*, vol. 2018, no. 1, pp. 287–294, 2018, doi: 10.1093/emph/eoy033.
- [111] L. P. van der Heide, G. M. J. Ramakers, and M. P. Smidt, 'Insulin signaling in the central nervous system: learning to survive', *Prog. Neurobiol.*, vol. 79, no. 4, pp. 205–221, Jul. 2006, doi: 10.1016/j.pneurobio.2006.06.003.
- [112] W. E. Sonntag *et al.*, 'Insulin-like growth factor-1 in CNS and cerebrovascular aging', *Front Aging Neurosci*, vol. 5, Jul. 2013, doi: 10.3389/fnagi.2013.00027.
- [113] E. Cohen *et al.*, 'Reduced IGF-1 signaling delays age-associated proteotoxicity in mice', *Cell*, vol. 139, no. 6, pp. 1157–1169, Dec. 2009, doi: 10.1016/j.cell.2009.11.014.
- [114] S. Gubbi, G. F. Quipildor, N. Barzilai, D. M. Huffman, and S. Milman, '40 YEARS of IGF1: IGF1: the Jekyll and Hyde of the aging brain', *Journal of Molecular Endocrinology*, vol. 61, no. 1, pp. T171–T185, Jul. 2018, doi: 10.1530/JME-18-0093.
- [115] A. Bartke and H. Brown-Borg, 'Life extension in the dwarf mouse', *Curr. Top. Dev. Biol.*, vol. 63, pp. 189–225, 2004, doi: 10.1016/S0070-2153(04)63006-7.

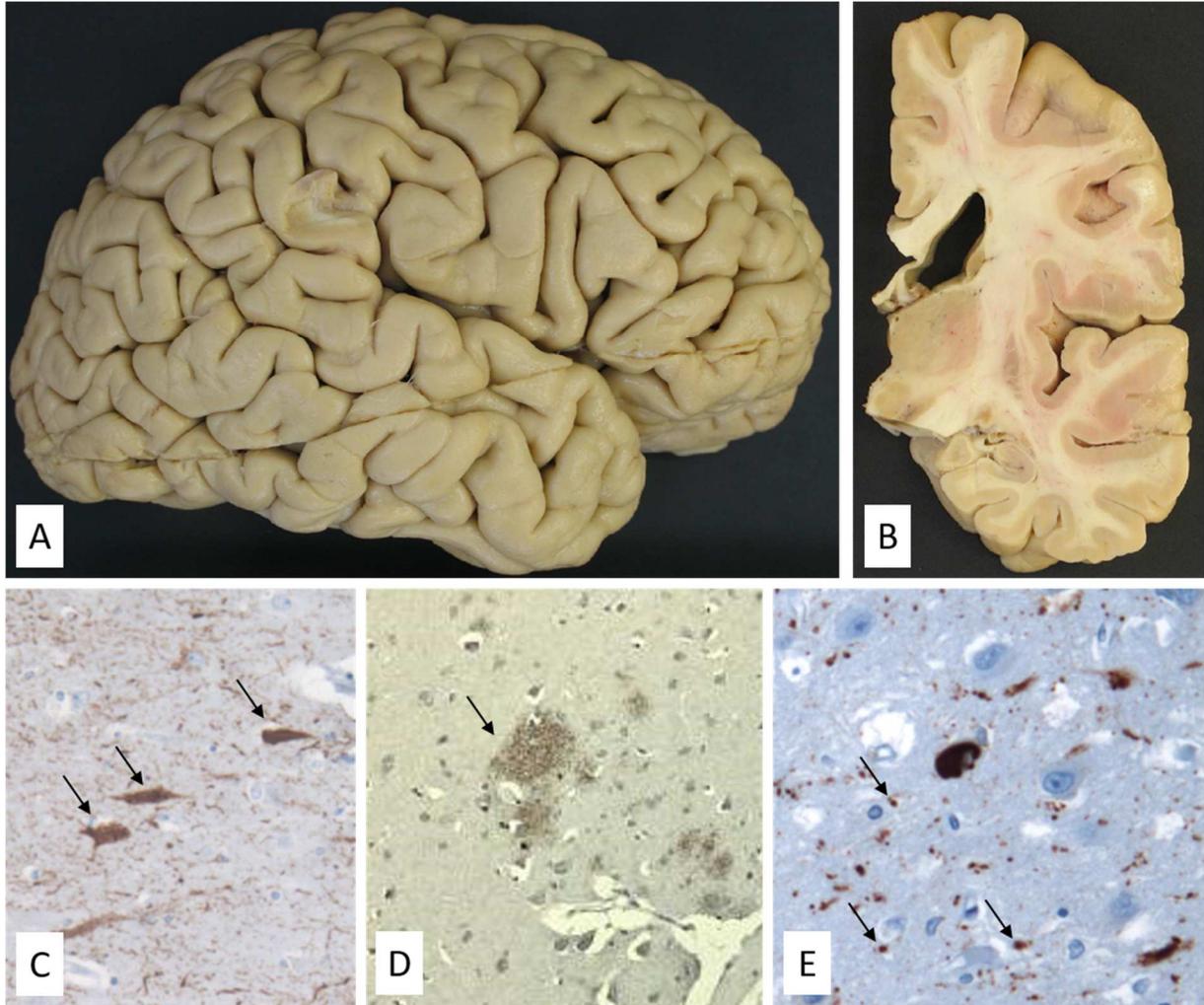
- [116] H. M. Brown-Borg, K. E. Borg, C. J. Meliska, and A. Bartke, 'Dwarf mice and the ageing process', *Nature*, vol. 384, no. 6604, p. 33, Nov. 1996, doi: 10.1038/384033a0.
- [117] K. Flurkey, J. Papaconstantinou, R. A. Miller, and D. E. Harrison, 'Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production', *Proc Natl Acad Sci U S A*, vol. 98, no. 12, pp. 6736–6741, Jun. 2001, doi: 10.1073/pnas.111158898.
- [118] M. A. Pappolla, R. Omar, and B. Saran, 'The "normal" brain. "Abnormal" ubiquitinated deposits highlight an age-related protein change.', *Am J Pathol*, vol. 135, no. 4, pp. 585–591, Oct. 1989.
- [119] P. Yin *et al.*, 'Aged monkey brains reveal the role of ubiquitin-conjugating enzyme UBE2N in the synaptosomal accumulation of mutant huntingtin', *Hum. Mol. Genet.*, vol. 24, no. 5, pp. 1350–1362, Mar. 2015, doi: 10.1093/hmg/ddu544.
- [120] S. H. Graham and H. Liu, 'Life and death in the trash heap: The ubiquitin proteasome pathway and UCHL1 in brain aging, neurodegenerative disease and cerebral Ischemia', *Ageing Res. Rev.*, vol. 34, pp. 30–38, Mar. 2017, doi: 10.1016/j.arr.2016.09.011.
- [121] A. N. Hegde, S. G. Smith, L. M. Duke, A. Pourquoi, and S. Vaz, 'Perturbations of Ubiquitin-Proteasome-Mediated Proteolysis in Aging and Alzheimer's Disease', *Front. Aging Neurosci.*, vol. 11, 2019, doi: 10.3389/fnagi.2019.00324.
- [122] É. Kevei and T. Hoppe, 'Ubiquitin sets the timer: impacts on aging and longevity', *Nature Structural & Molecular Biology*, vol. 21, no. 4, pp. 290–292, Apr. 2014, doi: 10.1038/nsmb.2806.
- [123] J. N. Keller, J. Gee, and Q. Ding, 'The proteasome in brain aging', *Ageing Research Reviews*, vol. 1, no. 2, pp. 279–293, Apr. 2002, doi: 10.1016/S1568-1637(01)00006-X.
- [124] S. Grimm, A. Hoehn, K. J. Davies, and T. Grune, 'Protein oxidative modifications in the aging brain: consequence for the onset of neurodegenerative disease', *Free Radic Res*, vol. 45, no. 1, pp. 73–88, Jan. 2011, doi: 10.3109/10715762.2010.512040.
- [125] C. D. Smith *et al.*, 'Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease.', *Proc Natl Acad Sci U S A*, vol. 88, no. 23, pp. 10540–10543, Dec. 1991.
- [126] R. J. Ward, F. A. Zucca, J. H. Duyn, R. R. Crichton, and L. Zecca, 'The role of iron in brain ageing and neurodegenerative disorders', *Lancet Neurol*, vol. 13, no. 10, pp. 1045–1060, Oct. 2014, doi: 10.1016/S1474-4422(14)70117-6.
- [127] A. Moreno-García, A. Kun, O. Calero, M. Medina, and M. Calero, 'An Overview of the Role of Lipofuscin in Age-Related Neurodegeneration', *Front Neurosci*, vol. 12, Jul. 2018, doi: 10.3389/fnins.2018.00464.
- [128] T. Grune, T. Jung, K. Merker, and K. J. A. Davies, 'Decreased proteolysis caused by protein aggregates, inclusion bodies, plaques, lipofuscin, ceroid, and "aggresomes" during oxidative stress, aging, and disease', *The International Journal of Biochemistry & Cell Biology*, vol. 36, no. 12, pp. 2519–2530, Dec. 2004, doi: 10.1016/j.biocel.2004.04.020.
- [129] E. Augé, I. Cabezón, C. Pelegrí, and J. Vilaplana, 'New perspectives on corpora amylacea in the human brain', *Scientific Reports*, vol. 7, no. 1, pp. 1–10, Feb. 2017, doi: 10.1038/srep41807.
- [130] M. Frimat, M. Daroux, R. Litke, R. Nevière, F. J. Tessier, and E. Boulanger, 'Kidney, heart and brain: three organs targeted by ageing and glycation', *Clin. Sci.*, vol. 131, no. 11, pp. 1069–1092, Jun. 2017, doi: 10.1042/CS20160823.
- [131] J. C. Kohn, M. C. Lampi, and C. A. Reinhart-King, 'Age-related vascular stiffening: causes and consequences', *Front Genet*, vol. 6, Mar. 2015, doi: 10.3389/fgene.2015.00112.

- [132] V. M. Monnier *et al.*, ‘Cross-linking of the extracellular matrix by the maillard reaction in aging and diabetes: an update on “a puzzle nearing resolution”’, *Ann. N. Y. Acad. Sci.*, vol. 1043, pp. 533–544, Jun. 2005, doi: 10.1196/annals.1333.061.
- [133] J. Chaudhuri *et al.*, ‘The Role of Advanced Glycation End Products in Aging and Metabolic Diseases: Bridging Association and Causality’, *Cell Metab.*, vol. 28, no. 3, pp. 337–352, Sep. 2018, doi: 10.1016/j.cmet.2018.08.014.
- [134] K. Janda *et al.*, ‘Vascular Effects of Advanced Glycation End-Products: Content of Immunohistochemically Detected AGEs in Radial Artery Samples as a Predictor for Arterial Calcification and Cardiovascular Risk in Asymptomatic Patients with Chronic Kidney Disease’, *Dis Markers*, vol. 2015, 2015, doi: 10.1155/2015/153978.
- [135] T. Teissier and É. Boulanger, ‘The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging’, *Biogerontology*, Apr. 2019, doi: 10.1007/s10522-019-09808-3.
- [136] D. Osgood, M. C. Miller, A. A. Messier, L. Gonzalez, and G. D. Silverberg, ‘Aging alters mRNA expression of amyloid transporter genes at the blood-brain barrier’, *Neurobiol Aging*, vol. 57, pp. 178–185, Sep. 2017, doi: 10.1016/j.neurobiolaging.2017.05.011.
- [137] C. Iannuzzi, G. Irace, and I. Sirangelo, ‘Differential effects of glycation on protein aggregation and amyloid formation’, *Front Mol Biosci*, vol. 1, p. 9, 2014, doi: 10.3389/fmolb.2014.00009.
- [138] H. J. Aizenstein *et al.*, ‘Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly’, *Arch Neurol*, vol. 65, no. 11, pp. 1509–1517, Nov. 2008, doi: 10.1001/archneur.65.11.1509.
- [139] S. Haller *et al.*, ‘Amyloid Load, Hippocampal Volume Loss, and Diffusion Tensor Imaging Changes in Early Phases of Brain Aging’, *Front. Neurosci.*, vol. 13, 2019, doi: 10.3389/fnins.2019.01228.
- [140] M. Schröder and R. J. Kaufman, ‘ER stress and the unfolded protein response’, *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 569, no. 1, pp. 29–63, Jan. 2005, doi: 10.1016/j.mrfmmm.2004.06.056.
- [141] M. K. Brown and N. Naidoo, ‘The endoplasmic reticulum stress response in aging and age-related diseases’, *Front Physiol*, vol. 3, p. 263, 2012, doi: 10.3389/fphys.2012.00263.
- [142] G. Martínez, C. Duran-Aniotz, F. Cabral-Miranda, J. P. Vivar, and C. Hetz, ‘Endoplasmic reticulum proteostasis impairment in aging’, *Aging Cell*, vol. 16, no. 4, pp. 615–623, Aug. 2017, doi: 10.1111/acel.12599.
- [143] M. P. Mattson and T. V. Arumugam, ‘Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States’, *Cell Metab*, vol. 27, no. 6, pp. 1176–1199, Jun. 2018, doi: 10.1016/j.cmet.2018.05.011.
- [144] D. Harman, ‘THE FREE RADICAL THEORY OF AGING: EFFECT OF AGE ON SERUM COPPER LEVELS’, *J Gerontol*, vol. 20, pp. 151–153, Apr. 1965.
- [145] D. R. Green, L. Galluzzi, and G. Kroemer, ‘Mitochondria and the autophagy-inflammation-cell death axis in organismal aging’, *Science*, vol. 333, no. 6046, pp. 1109–1112, Aug. 2011, doi: 10.1126/science.1201940.
- [146] R. X. Santos *et al.*, ‘Mitochondrial DNA oxidative damage and repair in aging and Alzheimer’s disease’, *Antioxid. Redox Signal.*, vol. 18, no. 18, pp. 2444–2457, Jun. 2013, doi: 10.1089/ars.2012.5039.
- [147] A. K. Pollard, E. L. Craig, and L. Chakrabarti, ‘Mitochondrial Complex 1 Activity Measured by Spectrophotometry Is Reduced across All Brain Regions in Ageing and More Specifically in Neurodegeneration’, *PLoS ONE*, vol. 11, no. 6, p. e0157405, 2016, doi: 10.1371/journal.pone.0157405.

- [148] J. Yao, R. T. Hamilton, E. Cadenas, and R. D. Brinton, 'Decline in mitochondrial bioenergetics and shift to ketogenic profile in brain during reproductive senescence', *Biochim. Biophys. Acta*, vol. 1800, no. 10, pp. 1121–1126, Oct. 2010, doi: 10.1016/j.bbagen.2010.06.002.
- [149] S. Lores-Arnaiz, P. Lombardi, A. G. Karadayan, F. Orgambide, D. Cicerchia, and J. Bustamante, 'Brain cortex mitochondrial bioenergetics in synaptosomes and non-synaptic mitochondria during aging', *Neurochem. Res.*, vol. 41, no. 1–2, pp. 353–363, Feb. 2016, doi: 10.1007/s11064-015-1817-5.
- [150] B. A. I. Payne and P. F. Chinnery, 'Mitochondrial dysfunction in aging: Much progress but many unresolved questions', *Biochim Biophys Acta*, vol. 1847, no. 11, pp. 1347–1353, Nov. 2015, doi: 10.1016/j.bbabi.2015.05.022.
- [151] A. Trifunovic and N.-G. Larsson, 'Mitochondrial dysfunction as a cause of ageing', *J. Intern. Med.*, vol. 263, no. 2, pp. 167–178, Feb. 2008, doi: 10.1111/j.1365-2796.2007.01905.x.
- [152] N. Braidy *et al.*, 'Mapping NAD(+) metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence', *Biogerontology*, vol. 15, no. 2, pp. 177–198, Apr. 2014, doi: 10.1007/s10522-013-9489-5.
- [153] E. F. Fang *et al.*, 'NAD+ in Aging: Molecular Mechanisms and Translational Implications', *Trends Mol Med*, vol. 23, no. 10, pp. 899–916, 2017, doi: 10.1016/j.molmed.2017.08.001.
- [154] G. Kroemer, L. Galluzzi, and C. Brenner, 'Mitochondrial membrane permeabilization in cell death', *Physiol. Rev.*, vol. 87, no. 1, pp. 99–163, Jan. 2007, doi: 10.1152/physrev.00013.2006.
- [155] A. Raffaello and R. Rizzuto, 'Mitochondrial longevity pathways', *Biochim. Biophys. Acta*, vol. 1813, no. 1, pp. 260–268, Jan. 2011, doi: 10.1016/j.bbamer.2010.10.007.
- [156] C. Correia-Melo *et al.*, 'Mitochondria are required for pro-ageing features of the senescent phenotype', *EMBO J.*, vol. 35, no. 7, pp. 724–742, Apr. 2016, doi: 10.15252/embj.201592862.
- [157] A. Mandal and C. M. Drerup, 'Axonal Transport and Mitochondrial Function in Neurons', *Front. Cell. Neurosci.*, vol. 13, 2019, doi: 10.3389/fncel.2019.00373.
- [158] W. Guo, K. Stoklund Dittlau, and L. Van Den Bosch, 'Axonal transport defects and neurodegeneration: Molecular mechanisms and therapeutic implications', *Seminars in Cell & Developmental Biology*, Sep. 2019, doi: 10.1016/j.semcdb.2019.07.010.
- [159] S. A. Small, W. Y. Tsai, R. DeLaPaz, R. Mayeux, and Y. Stern, 'Imaging hippocampal function across the human life span: is memory decline normal or not?', *Ann. Neurol.*, vol. 51, no. 3, pp. 290–295, Mar. 2002, doi: 10.1002/ana.10105.
- [160] A. Navarro *et al.*, 'Hippocampal mitochondrial dysfunction in rat aging', *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 294, no. 2, pp. R501–509, Feb. 2008, doi: 10.1152/ajpregu.00492.2007.
- [161] R. A. Nixon, 'The role of autophagy in neurodegenerative disease', *Nat. Med.*, vol. 19, no. 8, pp. 983–997, Aug. 2013, doi: 10.1038/nm.3232.
- [162] T. Hara *et al.*, 'Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice', *Nature*, vol. 441, no. 7095, pp. 885–889, Jun. 2006, doi: 10.1038/nature04724.
- [163] M. Komatsu *et al.*, 'Loss of autophagy in the central nervous system causes neurodegeneration in mice', *Nature*, vol. 441, no. 7095, pp. 880–884, Jun. 2006, doi: 10.1038/nature04723.
- [164] D.-S. Yang *et al.*, 'Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits', *Brain*, vol. 134, no. Pt 1, pp. 258–277, Jan. 2011, doi: 10.1093/brain/awq341.

- [165] H. Wang, R. Wang, I. Carrera, S. Xu, and M. K. Lakshmana, 'TFEB Overexpression in the P301S Model of Tauopathy Mitigates Increased PHF1 Levels and Lipofuscin Puncta and Rescues Memory Deficits', *eNeuro*, vol. 3, no. 2, Apr. 2016, doi: 10.1523/ENEURO.0042-16.2016.
- [166] A. Lopez *et al.*, 'A152T tau allele causes neurodegeneration that can be ameliorated in a zebrafish model by autophagy induction', *Brain*, vol. 140, no. 4, pp. 1128–1146, Apr. 2017, doi: 10.1093/brain/awx005.
- [167] F. Yang *et al.*, 'mTOR and autophagy in normal brain aging and caloric restriction ameliorating age-related cognition deficits', *Behav. Brain Res.*, vol. 264, pp. 82–90, May 2014, doi: 10.1016/j.bbr.2014.02.005.
- [168] M. Shibata *et al.*, 'Regulation of intracellular accumulation of mutant Huntingtin by Beclin 1', *J. Biol. Chem.*, vol. 281, no. 20, pp. 14474–14485, May 2006, doi: 10.1074/jbc.M600364200.
- [169] D. A. Loeffler, 'Influence of Normal Aging on Brain Autophagy: A Complex Scenario', *Front. Aging Neurosci.*, vol. 11, 2019, doi: 10.3389/fnagi.2019.00049.
- [170] R. Chandran *et al.*, 'Cellular calcium signaling in the aging brain', *Journal of Chemical Neuroanatomy*, vol. 95, pp. 95–114, Jan. 2019, doi: 10.1016/j.jchemneu.2017.11.008.
- [171] E. C. Toescu, A. Verkhratsky, and P. W. Landfield, 'Ca²⁺ regulation and gene expression in normal brain aging', *Trends in Neurosciences*, vol. 27, no. 10, pp. 614–620, Oct. 2004, doi: 10.1016/j.tins.2004.07.010.
- [172] E. C. Toescu, 'Altered Calcium Homeostasis in Old Neurons', in *Brain Aging: Models, Methods, and Mechanisms*, D. R. Riddle, Ed. Boca Raton (FL): CRC Press/Taylor & Francis, 2007.
- [173] O. Thibault and P. W. Landfield, 'Increase in single L-type calcium channels in hippocampal neurons during aging', *Science*, vol. 272, no. 5264, pp. 1017–1020, May 1996, doi: 10.1126/science.272.5264.1017.
- [174] O. Thibault, R. Hadley, and P. W. Landfield, 'Elevated postsynaptic [Ca²⁺]_i and L-type calcium channel activity in aged hippocampal neurons: relationship to impaired synaptic plasticity', *J. Neurosci.*, vol. 21, no. 24, pp. 9744–9756, Dec. 2001.
- [175] J. C. Gant, M. M. Sama, P. W. Landfield, and O. Thibault, 'Early and Simultaneous Emergence of Multiple Hippocampal Biomarkers of Aging Is Mediated by Ca²⁺-Induced Ca²⁺ Release', *J. Neurosci.*, vol. 26, no. 13, pp. 3482–3490, Mar. 2006, doi: 10.1523/JNEUROSCI.4171-05.2006.
- [176] R. F. Feissner, J. Skalska, W. E. Gaum, and S.-S. Sheu, 'Crosstalk signaling between mitochondrial Ca²⁺ and ROS', *Front Biosci.*, vol. 14, pp. 1197–1218, Jan. 2009.
- [177] D. Murchison and W. H. Griffith, 'Age-related alterations in caffeine-sensitive calcium stores and mitochondrial buffering in rat basal forebrain', *Cell Calcium*, vol. 25, no. 6, pp. 439–452, Jun. 1999, doi: 10.1054/ceca.1999.0048.
- [178] M. L. Michaelis *et al.*, 'Decreased plasma membrane calcium transport activity in aging brain', *Life Sciences*, vol. 59, no. 5, pp. 405–412, Jul. 1996, doi: 10.1016/0024-3205(96)00319-0.
- [179] J. Xiong, A. Verkhratsky, and E. C. Toescu, 'Changes in Mitochondrial Status Associated with Altered Ca²⁺ Homeostasis in Aged Cerebellar Granule Neurons in Brain Slices', *J. Neurosci.*, vol. 22, no. 24, pp. 10761–10771, Dec. 2002, doi: 10.1523/JNEUROSCI.22-24-10761.2002.
- [180] C. Geula *et al.*, 'Loss of calbindin-D28k from aging human cholinergic basal forebrain: relation to neuronal loss', *J. Comp. Neurol.*, vol. 455, no. 2, pp. 249–259, Jan. 2003, doi: 10.1002/cne.10475.

Figure 1: Illustration of common histological changes during normal brain ageing



Legend:

A: Gross morphology of a formalin-fixed post mortem brain hemisphere from a 85-yo man without any cognitive decline. Note the very subtle and diffuse cortical atrophy and the preservation of most associative cortical areas. B: Coronal view from the same brain specimen. Note the absence of significant atrophy of the hippocampus. C: Sparse neurofibrillary tangles (arrows) in the hippocampus of the same patient (Tau protein immunohistochemistry). D: Diffuse cortical amyloid deposits in the same case (arrow). Note the absence of senile plaque (β -amyloid immunohistochemistry). E: Isolated argyrophilic grains (arrows) in the hippocampus of a 86-yo cognitively normal woman (Tau protein immunohistochemistry).

Figure 2: estimated prevalence of amyloid deposits and neurofibrillary pathology according to the age of the subjects

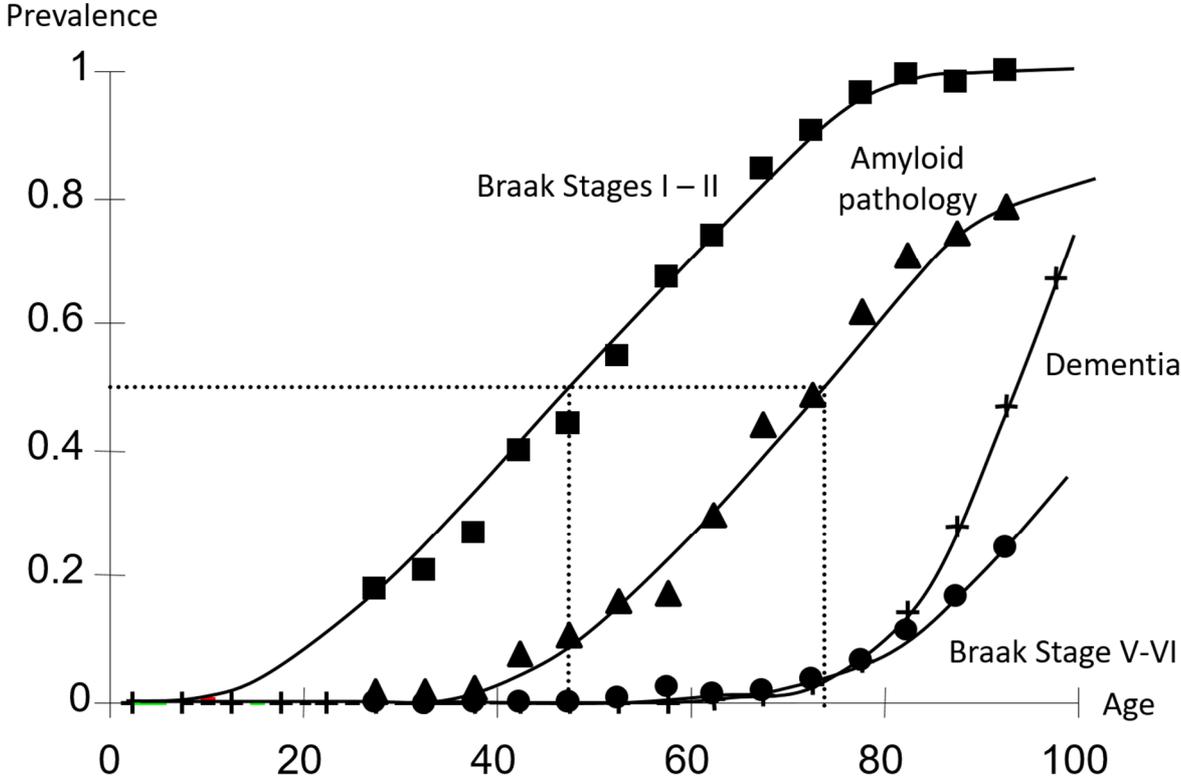


Table 1. Gene expression changes over time in the ageing human brain

Gene category	Expression
Mitochondrial function	↘
Neural plasticity/Synapses	↘
Inhibitory interneurons	↘
Ubiquitin-proteasome system	↘
Stress response	↗
Immune/inflammatory response	↗
Metal ion homeostasis	↗
Myelin-related functions	↗
Glia	↗