REVIEW ARTICLE

Regional –and cell type– specific changes of the human brain during aging

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Abstract: As individuals age, cognitive decline becomes more prominent, concomitant with an elevated susceptibility to neurodegenerative diseases and dementia. Additionally, symptoms of chronic neuropsychiatric diseases tend to worsen with age. It is crucial to highlight that the aging process does not affect individuals uniformly, and its effects can vary, even within the same person. This review aims to summary the impact of healthy aging on the human brain, focusing on the variations from different brain regions and cell types. Depending on specific brain regions, the brain exhibits thinning, volume reduction, regional shrinkage, disrupted tissue integrity, decreased cell complexity, or iron accumulation during aging. Moreover, the brain cells exhibit morphology and function changes during aging. Neurons undergo changes characterized by reduced dendrites, dendritic spines, and axons with less compact myelin sheaths, leading to a significant loss of synapses. Comparatively, glia often transform into a reactive phenotype.

Keywords: human brain; brain regions; brain cell types; aging.

INTRODUCTION

Certain organs, such as the skin or liver, exhibit a high regenerative capacity, allowing them to maintain or restore organ size and function. In contrast, tissues like the heart may have more limited regenerative capabilities after damage. Cai *et al.* investigated the impact of aging on the regenerative capacity of various tissues in mice, including liver, muscle, skin, vessels, small intestine, lung, and heart. Their findings revealed a higher and sustained level of chronic inflammation, compromised stem cell activation after injury, and impaired angiogenesis capacity in aged mice across different organs.[1] Overall, aging leads to a sharp decrease in the regenerative capacity of most organs.

The effect of aging on the human brain can negatively affect older adult performance in many aspects, such as motor control[2-4], sensory perception[5-7], decision making[8-11], emotional regulation[8-11], and memory and learning[12-18]. As our brain ages, cognitive decline becomes more prevalent, and the risk of neurodegenerative diseases and dementia increases. Additionally, symptoms of chronic neuropsychiatric diseases tend to worsen with age. However, it is essential to underscore that the aging process does not affect individuals uniformly, and its effects can vary even within the same person. In this review, we aim to discuss the diverse effects of human brain aging on various brain regions and cell types.

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1. EFFECTS OF HUMAN BRAIN AGING ON VARIOUS BRAIN REGIONS

Brain structure changes throughout the lifespan, even in the context of healthy aging.[19] Irrespective of the methods used, most studies observed that the brain undergoes volumetric reduction, accompanied by an increase in size and depth of sulci as individuals age.[20] In healthy aging, the human brain experiences a decline in volume at a rate of 0.2% per year starting at the age of 35. This reduction rate gradually increases to 0.5% per year by the age of 60.[21, 22] Estimates suggest that the brain loses approximately 10% of its maximum achieved weight in older adults by the age of 75,[20] increasing up to 13% by the age of 90.[23, 24] The volumetric reduction observed in various brain regions as a result of aging does not occur uniformly.[20] Significant alterations were most pronounced in the frontal and temporal cortex regions, with subsequent notable changes in the putamen and thalamus.[19] It was also found that the shrinkage and reduction of synaptic spines, along with a decline in the number of synapses, are major contributors to the loss in total brain volume, with neuronal loss accounting for a smaller proportion.[19]

1.1. Gray matter and white matter

Both the gray and white matter decreases in volume in the prefrontal cortex (PFC), medial temporal and parietal cortex during aging,[22] which would explain the worse cognitive performance in older adults. However, they do not decrease in volume at the same rate.[20] Gray matter decreases steadily throughout the lifespan, while white matter increases in volume until the mid-50s, after which it declines at an accelerated rate.[24-26] Gray matter loss initiates early in life[27, 28] and is more prominent in the cortex than in subcortical structures,[29] with the frontal lobe's gray matter being most associated with aging.[20] Cerebral and cerebellar white matter loss starts later but to a greater extent. It was estimated that, on average, 14% of the cerebral cortex, 35% of the hippocampus, and 26% of cerebral white matter are lost between the ages of 30 to 90.[24] The frontal and temporal lobes experience greater white matter loss due to aging compared to other areas.[30]

1.2. Cortical regions

1.2.1. Frontal area

The frontal lobes, constituting two-thirds of the human brain, play a pivotal role in motor function and cognitive processes such as attention, memory, and language.[31] Extensive cortical thinning has been observed in the frontal regions, such as a correlation between epigenetic/chronological age and volume reduction, especially in the superior frontal area.[32] Others indicated that the age-related decline in working memory among older adults without cognitive impairment is moderated by structural changes in the orbitofrontal gyrus and other frontal regions.[33] The frontal pole, or Brodmann area (BA) 10, is responsible for various functions such as decision-making, odor evaluation, and working memory.[34, 35] Although the effect of aging was not associated with total volume change, a reduction in gray matter density was found.[36]

PFC is critical for multiple cognitive capabilities, such as working memory, attention, and multitasking abilities.[22] Age-related declines in working memory, learning, and attention are thought to result from a reduction in inhibitory control among older adults.[37] This decline has been associated with structural and functional changes in the PFC.[22,38] In addition, older adults can compensate for brain regional decline by employing additional cognitive resources to maintain performance.[22] Increased PFC activity in older adults may compensate for the decline in perceptual processes caused by decreased occipital cortex activities.[39] Moreover, older adults can utilize contralateral regions of the PFC to carry out high cognitive-demanding tasks, compensating for the use of unilateral PFC in younger adults.[22,40]

1.2.2. Temporal area

The medial temporal lobe is crucial for declarative memory, involving conscious recollection of facts and events.[41] Studies show positive correlations between specific regions in this lobe and cognitive abilities like episodic memory.[42] Bilateral temporal areas experience widespread cortical thinning, especially in the left temporal cortex, which is sensitive to advanced epigenetic age. Notably, advanced epigenetic age is linked to reduced volume in the ventromedial temporal areas.[43] Additionally, individuals with dementia or cognitive impairment with aging are more likely to show alterations in

the medial temporal lobe.[44] The temporal pole, or BA38, is associated with several cognitive functions such as facial recognition, naming, and autobiographic memory.[45, 46] An average of 16 to 22% volumetric decline in the temporal pole was found as part of healthy aging.[47]

1.2.3. Parietal area

The anterior parietal cortex in humans houses primary somatosensory areas, while the posterior parietal cortex serves higher-order functions.[48] Parietal regions undergo widespread cortical thinning and volume reduction with advanced chronological age.[49] In a comparison between adult and younger samples, the ratio of parietal lobe cortex to white matter was greater in female brains. Notably, male brains showed essentially no decrease in surface area over time, while female brains exhibited a significant decrease.[50]

1.2.4. Occipital area

The occipital lobe, a vital region of the central nervous system (CNS), plays a pivotal role in the sense of vision.[51] Resting-state brain activities in the occipital region increase with aging, potentially contributing to subjective memory decline.[52] Cortical thinning is observable in occipital regions, and advanced epigenetic age correlates with volume reduction in the right occipital areas.[43] Additionally, the impact of blue light on brain responses diminishes with aging, particularly in areas implicated in visual functions and crucial regions for alertness regulation and higher executive processes. This suggests a potential decrease in the effect of blue light in occipital cortices among elderly individuals.[53]

1.2.5. Insular cortex

The insular cortex, often referred to as the 'Island of Reil', is situated deep within the lateral sulcus of the brain. With its involvement in a diverse range of functions, from sensory and affective processing to high-level cognition, the insula plays a crucial role in human neurobiology.[54] Research suggests that healthy aging is characterized by a loss of complexity in the frontal and parietal lobes and an increased complexity in the insula, limbic, and temporal lobes.[55] In terms of surface area, the anterior left insula region exhibits a negative association with advanced epigenetic age. Concurrently, advanced chronological age contributes to cortical thinning in the superior insular region.[43]

1.2.6. Orbital gyrus

The posterior orbital gyrus, responsible for processing olfactory and gustatory inputs and integrating emotions and memories associated with sensory experiences, receives inputs from limbic regions.[56] Notably, researchers indicated that older epigenetic age is correlated with reduced volume in the bilateral orbital regions.[43]

1.2.7. Olfactory bulb

The olfactory bulb (OB) is located at the inferior side of the brain, responsible for receiving and processing olfactory information, relaying it to amygdala, hippocampus and orbitofrontal cortex to be further processed. The decline of olfactory function is commonly found in older adults, and OB tau pathology is regarded as part of normal aging.[57] In older adults, the turnover of interneurons[58] and innervation of the ventral half of OB decreases.[59] OB also becomes thinner and the number of mitral cells decreases significantly.[60]

1.3. Subcortical regions

1.3.1. Limbic system

The limbic system is the part of the brain involved in our behavioral and emotional responses, especially when it comes to behaviors for survival. The anatomical components of the limbic system include hippocampus, parahippocampal gyrus, cingulate gyrus, pineal gland, fornix, corpus callosum, thalamus, hypothalamus, mammillary body, and amygdala.

The hippocampus plays an important role in learning, formation and consolidation of memory, as well as regulation of emotions like fear, anxiety, and stress. The hippocampus shrinks with age[24, 61, 62] but there is no corresponding reduction in principal cell numbers, dendritic branching, and dendritic spine density.[63, 64]

The parahippocampal gyrus, especially its entorhinal and perirhinal subdivisions, is particularly susceptible to pathological changes associated with Alzheimer's disease (AD), serving as focal points for disease onset and experiencing the most significant cortical damage.[65] Elderly adults demonstrated

reduced activation in the parahippocampal gyrus compared to younger counterparts.[66] The parahippocampal cortex emerges as a potential key factor in age-related differences in navigational performance. Specifically, only young adults exhibited significant activation in the bilateral hippocampus and left parahippocampal gyrus, while older adults showed no activation in the hippocampal/parahippocampal region.[67]

The cingulate cortex is integral to the connectivity and functioning of various cognitive processes, including emotion, action, and memory. Specifically, the anterior cingulate cortex (ACC) plays a key role in processing information from the orbitofrontal cortex regarding reward and non-reward outcomes, while the posterior cingulate cortex receives spatial and action-related information from parietal cortical areas.[68] Simultaneously, ACC exhibits a bilateral attenuated U-shaped relationship with age.[69] Successful cognitive aging is associated with greater cortical thickness, particularly in the anterior cingulate and mid-cingulate cortices, as well as the medial temporal lobes.[70]

The pineal gland produces and secretes melatonin cyclically at night, based on the current light and dark cycle of the environment. Effects of aging on the pineal gland include vascular narrowing, hardening, a decrease in cell number, and a lower melatonin level.[71-76]

The fornix represents one of the earliest maturing white matter tracts. It comprises the principal efferent and afferent white matter tracts from the hippocampi, the status of which is presumed to play a role in age-related cognitive decline. Following its maturation peak in late adolescence, the fornix undergoes progressive atrophy throughout the lifespan.[77] Notably, older adult patients with AD exhibited a significant volume reduction in the fornix.[78]

The corpus callosum (CC) is the largest white matter nerve tract found in the human brain,[79] responsible for the communication and interaction between the two halves of the brain.[79, 80] The total volume, nerve fiber count and length, and white matter integrity of CC decrease with age, with earlier and more accelerated degradation onset observed at the anterior portion.[79, 81]

The thalamus, with its cortical, subcortical, and cerebellar connections, plays a crucial role as a central node in networks supporting cognitive functions such as memory, attention, and information processing. Reduced thalamic volume, particularly in the anterior and medial nuclei, is associated with older age, and the size of these nuclei correlates with episodic memory and executive functions, including speed of information processing, directed attention, and working memory. Additionally, at older age, there are higher mean diffusivity and lower fractional anisotropy in regions of the thalamus and its projections, particularly in thalamofrontal and thalamoparietal networks. These changes are linked to age-related differences in information processing between younger and older adults.[82]

The hypothalamus is versatile in regulating various functions, including body temperature, water and salt metabolism, food intake, sleep, reproduction, visceral activities and emotions.[76] The effect of aging on hypothalamus is similar to that on the pituitary gland, such as a decrease in overall mass and blood supply, as well as hyperplasia of connective tissue. Decrease in the release of gonadotropin-releasing hormone I, growth hormone-releasing hormones and thyroid-stimulating hormone-releasing hormones as well as monoamine neurotransmitters can also be observed in the older hypothalamus.[76, 83-88]

The mammillary bodies (MB) are a pair of small round bodies located at the undersurface of the brain. As a component of the extended hippocampal system, they play a role in the mnemonic process.[89,90] Atrophy of the MB is apparent in older adult patients with AD,[78,91] but not so in healthy individuals.[92]

The amygdala is an almond-shaped structure located within the temporal lobes, involved in fear, reward learning, and stress. The amygdala undergoes a non-uniform decrease in size, particularly at its lateral, basal, and accessory basal nuclei, as individuals age.[93,94] However, the amygdala volume is less effected by aging than other brain structures, such as the thalamus.[19]

1.3.2. Basal ganglia

The basal ganglia are a group of subcortical nuclei, mainly controlling the body's voluntary movements. They mainly include the caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nucleus.

The caudate nucleus, a 'C'-shaped subcortical structure near the thalamus, is crucial for higher neurological functions, body posture, limb control, and movement precision.[95,96] In both men and women, the caudate nucleus shrinks approximately 5% and 4%, respectively, with statistically significant

volume differences between genders. Both genders also show a significant rightward asymmetry in the caudate and putamen.[97] Furthermore, during aging, a negative correlation exists between hippocampal and caudate nucleus gray matter, suggesting a competitive interaction between these memory systems.[98]

The putamen, together with the caudate nucleus, shape the striatum. Traditionally linked to reinforcement learning and motor control, including speech articulation,[99] the putamen maintains constant mean volumes throughout the aging process.[100] However, iron accumulation was found in the putamen from older adult patients with various neurodegenerative disorders such as multiple sclerosis, AD, and amyotrophic lateral sclerosis.[101]

The globus pallidus (GP) comprises globus pallidus internus and globus pallidus externus. Dysfunction of GP has been observed in conditions such as ischemia, alcohol, and opiate abuse, leading to various cognitive and motor problems.[102] Although GP shows no statistically significant atrophy with age,[103] iron accumulation was also found in GP in various neurodegenerative disorders.[101]

The substantia nigra comprises the pars compacta, primarily housing dopaminergic cells, and the pars reticulata, mainly containing GABAergic cells.[104] Shrinkage of the substantia nigra is a part of aging process.[82, 105] In Parkinson's disease, motor dysfunction stems from dopaminergic neuron loss in the substantia nigra pars compacta, leading to dopamine depletion in the nigrostriatal pathway.[106] Drivers of nigral oxidative stress seen in healthy aging contribute to heightened oxidative stress in Parkinson's disease, suggesting an exacerbation of aging-related molecular pathways.[107]

The subthalamic nucleus is a small lens-shaped structure that is located at the junction of the midbrain and diencephalon. It contains glutaminergic neurons with projections to the GPi. In age-related tauopathy, the expression of tau was frequently detected in the subthalamus in post-mortem brain tissue.[108]

1.4. Cerebellum

The cerebellum is located at the bottom of brain, underneath the cerebral hemisphere. It is involved in a wide range of functions such as motor control, emotion control, learning and memory.[109] There is a strong negative correlation between cerebellar volume and age, which has been associated with cognitive and motor performance decline.[110] Reduction in gray matter volume as well as prominent DNA methylation have been identified in the cerebellum, leading to motor frailty in older adults.[110]

1.5. Brainstem

The brainstem is the stalk-like portion of the brain that connects the cerebrum and diencephalon with the spinal cord. It plays critical roles in regulating cardiac and respiratory function, providing motor and sensory nerve supply, and regulating the sleep cycle. It is composed of the midbrain, the pons, and the medulla oblongata. The midbrain includes superior colliculi, inferior colliculi, red nucleus, locus coeruleus, and other regions.

The superior colliculi (SC) is an evolutionarily conserved midbrain structure in mammals and plays vital roles in saccades, ocular-motor control, visual processing, and multi-sensory integration. The size and complexity of retinal ganglion cell arbors were found to diminish with age in the SC of rats.[111] In addition, a deleterious effect of aging was also found in complex audiovisual interactions in SC.[112]

The inferior colliculi (IC) is also a midbrain structure located just below SC. As part of the primary auditory pathway, it plays a vital role in auditory processing and sound localization.[113] The IC increases in size[114] but experiences a decrease in inhibitory neurons and neurotransmitters with age. Studies indicated altered sensitivity to sound regularities in the IC during aging.[115] Moreover, perineuronal nets in the IC, associated with structural and synaptic plasticity regulation, increase with age in rats.[116]

The Red Nucleus (RN), situated in the ventral midbrain, is a primitive brainstem structure. Between the ages of 9 and 30, there is a noticeable positive correlation between tissue regional transverse relaxation rates and age in the RN.[69] In addition, the association between the perivascular space and regional brain iron depositions in the RN was also found at age 75.

The Locus coeruleus (LC) is a nucleus that is located bilaterally in the brainstem. It is the main site for norepinephrine production, and its projections extend to and modulate cortical, subcortical, cerebellar, brainstem, and spinal cord circuits.[117] Although no significant change in the number or cell size of LC was observed during normal aging,[118] a marked reduction in noradrenergic neurons was reported in LC of AD patients.[119] The noradrenergic neurons in LC are believed to protect the brain against aging and neurodegenerative progression by influencing glial activities.[120]

Pons is a part of the brainstem located above the medulla oblongata and below the midbrain. It contains various motor and sensory nuclei[121] and is involved in the regulation of various functions such as facial sensation and movement, chewing and sleeping. There is no total volumetric loss[122-124] or white matter volume change found in pons in normal aging.[105,124] However, individual variability in volume change is notably influenced by gender.[125]

The medulla oblongata is located at the lower part of the brainstem, right above the spinal cord, and plays vital roles in the regulation of involuntary functions such as breathing, sneezing, heart rate, and blood pressure.[126] Normal aging has little effect on the volume change of medulla.[122-124] The structure and activity of neurons from multiple nuclei in the medulla also remain unchanged in aged mice.[127]

1.6. Cerebral blood vessels and meninges

The meninges refer to the membranous coverings of the brain and spinal cord and have three layers, the dura mater, arachnoid mater and pia mater. The circle of Willis is an important juncture that allows for proper blood flow from the arteries to both the front and back hemispheres of the brain.

The dura mater is made of a thick layer of dense connective tissue and is located directly underneath the skull. It is the outermost layer of the meninges that surrounds the brain and spinal cord. As people age, the attachment between the periosteal layer of the dura mater and the bones of the cranium becomes firmer, making the dura less pliable.[128] A negative correlation was also found between dura mater thickness and aging, with older adults having a significantly thinner dura.[129]

The arachnoid mater is one of the three meninge layers, located in between the dura and pia mater. It is responsible for cerebrospinal fluid (CSF) metabolism and circulation. The projection of arachnoid into the dura called the pacchionian granulation is specialized in transmitting CSF. With age, these granulations may become calcified, and their number and size increase.[130] The thickness of the arachnoid mater is positively correlated with age, and arachnoid mater hyperplasia is associated with aging.[131]

The circle of Willis (CW) is a ring-shaped arterial network located at the base of the brain and is responsible for the blood supply of the brain.[132] Based on autopsy studies, major arteries in the CW of older adults were found to be stenosis and atherosclerotic, with atherosclerotic plaque found in the majority of them.[132] Atherosclerosis is most commonly found in major arteries including the vertebral artery, the basilar artery, and the middle cerebral artery, but less so in smaller caliber arteries such as the posterior cerebral artery, anterior cerebral artery, or the communicating arteries.[133] However, such CW abnormalities were not strongly correlated to most of the neurodegenerative pathologies.

The effects of human brain aging on various brain regions are summarized in Fig. 1.

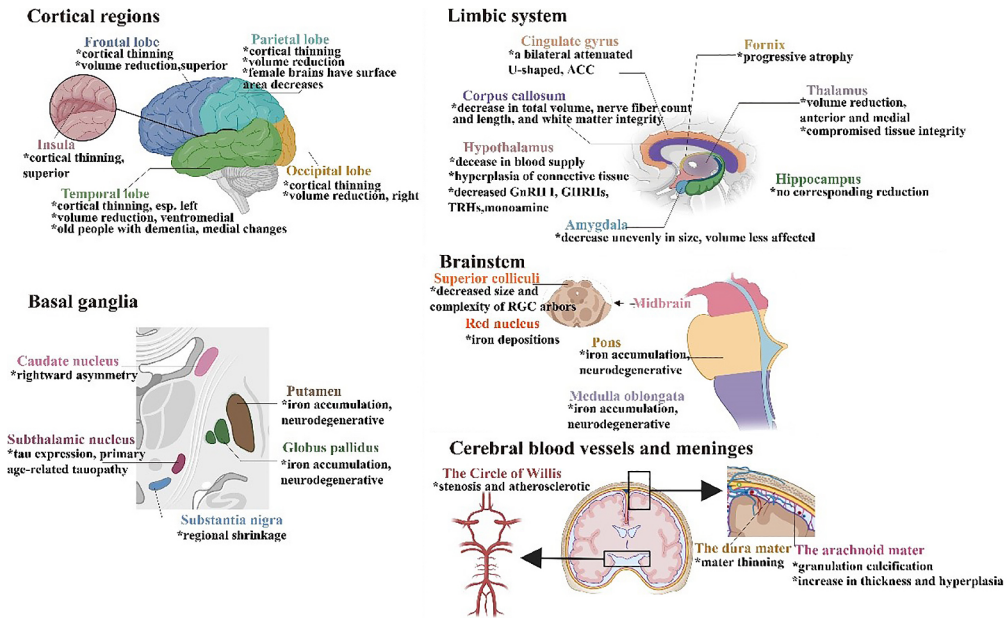

Figure 1. Effects of human brain aging on various brain regions.

For cortical regions, cortical thinning and volume reduction are frequently found in the frontal lobe, temporal lobe, parietal lobe, and occipital lobe during aging. For subcortical regions, the majority of the limbic system experiences a decrease in total volume or tissue integrity. For basal ganglia in the subcortical regions, globus pallidus and putamen show iron accumulation, while caudate and substantia nigra display regional shrinkage. For the brainstem, a decrease in cell complexity was observed in superior colliculi, and iron accumulation was found in the red nucleus, pons, and medulla oblongata, especially in aged people with neurodegenerative disorders. At last, the cerebral blood vessels and meninges also experience alterations during aging.

2. EFFECTS OF HUMAN BRAIN AGING ON VARIOUS BRAIN CELL TYPES

The brain contains a variety of cell types, mainly including neurons, astrocytes, microglia, oligodendrocytes, and endothelial cells. In this section, we focus on the effect of aging on the morphology and function changes of different brain cell types.

2.1. Neurons

There are over 86 billion neurons in the brain, divided into excitatory neurons that transmit and amplify signals, and inhibitory neurons that inhibit and refine those signals.[134, 135] With aging, the primary occurrence is neuronal atrophy rather than the loss of motor cortical neurons per se.[136] There is evidence of age-related differences, including reduced length of myelinated nerve fibers[137] and degeneration of pyramidal neurons.[138] Moreover, during normal aging, nerve cells undergo structural changes, including reduced dendrites and dendritic spines, decreased axons with less compact myelin sheaths, and a significant loss of synapses.[138] Additionally, age-related declines in dopaminergic neurotransmission result in increased neural noise, linked to the loss of dopaminergic neurons in the striatum.[139] Aging alters the interaction between glutamate, dopamine, and GABA[1407], potentially leading to increased neural noise due to excessively high levels of extracellular glutamate around neurons.[141] It has also been established that myelinated peripheral nerves in aged animals show axon loss, morphological irregularities, and a significant reduction in the expression of myelin and neurofilament genes and proteins.[142] Overall, the morphological and structural changes of neurons occur during aging.

Mitochondria are distributed in neurons' dendrites and axons,[143] crucial for cellular energy metabolism, Ca^{2+} homeostasis, and as a source of signals for regulating nuclear gene transcription.[144-146] Studies suggest neurons accumulate dysfunctional mitochondria during aging[147] due to an oxidative imbalance: increased production of reactive oxygen species and/or reduced antioxidant defenses, including superoxide anion radical, hydroxyl radical, and nitric oxide.[148] During aging, neurons also experience impaired autophagic and proteasomal degradation, leading to intracellular accumulation of autophagosomes with undegraded cargos, dysfunctional mitochondria, and abnormal proteins.[149-151] The lipid peroxidation product 4-hydroxynonenal can early impair lysosomes, contributing to the accumulation of damaged proteins and organelles and subsequent neuronal death.[152] Meanwhile, lipids can also accumulate in autophagic vesicles (lipofuscin) or lipid-laden vesicles.[153,154] The ubiquitin-proteasome pathway is essential for clearing abnormal proteins, and dysfunctions with normal aging, leading to the accumulation of protein aggregates in neurons associated with neurodegenerative diseases.[150] One hallmark of neuronal senescence is disrupted calcium homeostasis, adversely affecting neuronal physiology.[155,156] Synaptic Ca^{2+} signaling activates transcription factors, such as CREB and PGC-1α,[155,157] leading to the upregulation of genes involved in neuronal plasticity and stress resistance.[158] Aging undermines the ability of neurons to maintain physiological Ca^{2+} levels. Elevated cytoplasmic Ca^{2+} in aged neurons leads to dysregulated protein phosphorylation, cytoskeletal dynamics, and gene expression. Studies on hippocampal pyramidal neurons show that aging impairs Ca^{2+}-induced after-hyperpolarization, increasing Ca^{2+} influx and release.[156, 159-162] Studies on aged rats showed that impaired Ca^{2+} homeostasis is associated with age-related cognitive deficits.[163-165] Elevated intracellular Ca^{2+} levels can damage neurons through activation of Ca^{2+}-dependent proteases (calpains), triggering caspase-mediated apoptosis and PARP1-mediated cell death.[166-168] In addition, DNA damage in neurons increases with excitatory synaptic activity during aging.[169,170] Reduced hippocampal and olfactory neurogenesis in normal aging contribute to cognitive and olfactory deficits,[171] along with aging neural progenitor cells showing reduced mitochondrial oxidative metabolism.[172,173]

Together, besides the morphological and structural changes, aging also induces functional changes in neurons, including mitochondria dysfunction, oxidative damage, impaired protein homeostasis, dysregulated calcium homeostasis, abnormal DNA repair, and impaired neurogenesis.

2.2. Astrocytes

Astrocytes are the most abundant glial cells in the brain, supporting neurons, balancing the synaptic cleft content, and maintaining ion-homeostasis and blood-brain-barrier integrity. Dysfunctional astrocytes are implicated in neuropathology associated with both normal brain aging and age-related neurodegenerative diseases.[174] Studies in rodents, nonhuman primates, and humans have documented numerous aging-related morphological changes in astrocytes. These changes include increased expression of cytoskeletal proteins like glial fibrillary acidic protein, cell body hypertrophy, and a reduction in the number of long, slender processes.[107, 175-177]

Different external stressors have been shown to induce astrocyte senescence in vitro, including oxidative stress, proteasome inhibitors, and irradiation. Cultured human astrocytes exposed to stressors increased expression levels of established senescence markers, including p53, p21, and p16, along with the production of a senescence- associated secretory phenotype (SASP).[178-180] Importantly, senescent astrocytes can affect neuron vulnerability to glutamate-induced toxicity in vitro.[181] A recent study in aged individuals observed reduced lamin B1 levels and nuclear deformations in hippocampal astrocytes, suggesting an intraregional-dependent aging response in human astrocytes.[177] Aging astrocytes have been reported to exhibit increased reactivity, upregulating several genes previously associated with astrocytes responding to bacterial endotoxin lipopolysaccharide or ischemia.[182, 183] These studies have also documented the downregulation of several genes related to cholesterol synthesis, mitochondrial function, energy production, and antioxidant defense in aging astrocytes. Notably, aging astrocytes exhibited significant upregulation of genes related to the complement pathway, cytokines, and antigen presentation. These changes were predominantly observed in cerebellar, hippocampal, hypothalamic, and striatal astrocytes, with minimal differences noted in cortical astrocytes. Elimination of microglia-derived factors C1qα, TNF, and IL-1α resulted in the loss of many age-related changes in astrocyte reactivity, indicating that aging microglia contribute to the increase in astrocyte reactivity in the aging mouse CNS.[183] Additionally, region-specific differences in astrocyte aging were observed, for instance, cerebellar astrocytes upregulated proinflammatory genes like Casp1, Cxcl5, and Tlr4, while astrocytes from the visual cortex exhibited an increase in Bmp6.[184]

Together, aging astrocytes exhibit morphological and structural changes, including cell body hypertrophy, and decreased numbers of long, slender processes, as well as functional changes, including increased reactivity, decreased cholesterol synthesis, mitochondrial function, energy production, and antioxidant defense-related gene expression, increased the complement pathway, cytokines, and antigen presentation-related gene expression. Importantly, aging astrocytes exhibit region-specific differences.

2.3. Microglia

Microglia, the primary immune cells of the CNS, constitute a tissue-resident macrophage population with specific characteristics that support CNS health.[135,185,186] In their homeostatic adult state, resting microglia exhibit a highly ramified morphology, characterized by extended and arborized processes and a small soma.[187] However, in response to stimulation or during aging and CNS pathology, microglia undergo rapid changes in cell shape, gene expression, and functional behaviors, collectively known as microglial activation.[186, 188-190] As microglia age, they experience alterations in morphology, phenotype, and function.

Elevated levels of microglial activation are observed in the entorhinal cortex, hippocampal CA subfields, dentate gyrus, and subiculum of elderly nondemented individuals compared to adult controls.[191] The density of HLA-DR microglia in the white matter of cognitively normal older adults surpassed that of young adults and super-agers.[192] In females, the quantity of microglia in the neocortex exhibited an age-related increase, whereas in males, this pattern was not evident, despite the presence of 28% more neocortical glial cells.[2] In wild-type rodents, aged rats exhibited greater microglial activation in various brain regions, including the gray and white matter, corpus callosum, hippocampus, primary auditory cortex, and basal ganglia, compared to young animals.[193-195] Furthermore, the rate of microglial proliferation was higher in aged rats

than in their younger counterparts.[196,197] As for other spices such as aging canines, higher levels of Iba1 protein were observed in the dentate gyrus compared to adult canines, although microglia density did not vary with age.[198,199] Conversely, microglial activation was not observed in the brains of adult horses.[200]

In healthy brains, microglia remain resting, marked by a small cell body, fine processes, and a low expression of CD40, CD45, CD68, and MHC II.[201] Upon activation, microglia transition to an intermediate or amoeboid morphology, characterized by shorter, thicker processes, reduced arborization, and an enlarged cell soma.[59] Activated microglia express greater levels of immune-epitopes, such as CD40, CD45, CD68, CD11b, and CD11c.[197, 202-205] Aged human brains exhibit increased intermediate and amoeboid microglial morphologies in the neocortex and hippocampus. This is accompanied by elevated expression of CD68 and HLA-DR, markers for immune stimulation.[206-208] Moreover, microglial processes in the neocortex of aged individuals show reduced length, arborization area, and branching, indicative of glial activation.[189] Non-human primates (NHP), like humans, exhibit increased activation morphologies, dystrophic microglia, and HLA-DR/MHC II expression with aging. In marmosets, dystrophic microglia rise in the dorsal hippocampus.[209] Aged rodents show activation-related morphologic changes but lack dystrophic microglia seen in elderly humans and NHP.[210] Microarray analysis post lipopolysaccharide challenge in male mice showed increased CD68 and MHC II.[211] In old mice, CD68 mRNA and protein expression rose by over 50% in the corpus callosum and striatum compared to young mice.[212] Although aged microglia respond to an inflammatory challenge by producing higher levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, anti-inflammatory signatures have also been observed.[211,213-215] In aging microglia, lipid metabolism undergoes changes, leading to the accumulation of lipid droplets.[195] Lipid droplet-associated microglia exhibit phagocytosis deficits, increased ROS production, and elevated inflammatory cytokines.[216] Aged canine microglia show structural abnormalities, such as clustering, abnormal cytoplasm, fragmented, or tortuous processes, and occasional spheroidal swellings,[217] while old tree shrews display an increased number of ferritin-positive and dystrophic microglia compared to adults.[218]

In conclusion, microglia alterations in morphology, phenotype, and function with aging, including the transition to an intermediate or amoeboid morphology, with shorter, thicker processes, reduced arborization, and an enlarged cell soma, activation with pro-inflammatory cytokines as well as anti-inflammatory signatures.

2.4. Oligodendrocytes

Oligodendrocytes, originating from oligodendrocyte progenitor cells (OPCs), myelinate axons in the CNS.[219-221] A single oligodendrocyte can form multiple myelin internodes, facilitating rapid signal propagation and providing metabolic support to axons through monocarboxylate transporters, delivering lactate and pyruvate.[222]

Electron microscope studies of the aging rodent and NHP CNS reveal a loss in myelin integrity characterized by myelin decompaction and splits in the intraperiod and major dense lines.[138, 223-227] Multiphoton imaging in aging mice confirms myelin degeneration and internode elimination in the cortical upper layers.[228] The technical advancement of isolating and culturing OPCs from aged rodent brains has allowed several comparisons to be made between young adult and aging OPCs on transcriptional, proteomic, and functional levels.[229-232] Aging OPCs exhibit enriched transcripts linked to stem cell aging, such as mitochondrial dysfunction, inflammasome signaling, dysregulated nutrient sensing, autophagy, and unfolded protein response.[229,230] Aging OPCs also exhibit decreased levels of proteins involved in stem cell maintenance, DNA repair, cell cycle control, and chromatin remodeling.[231] Moreover, enzymes related to cholesterol synthesis were notably reduced, indicating a diminished capacity for cholesterol production during adulthood and aging. This is important as cholesterol is essential for the production of myelin.[231] Additionally, ion channels were identified to play a key role in OPC functional changes.[233] At the functional level, aging OPCs have a slower inherent ability to differentiate.[229] Aging oligodendrocytes show reduced expression of myelin protein genes (Mog, Plp, Cnp) and downregulation of the cholesterol synthesis gene (Hmgcs1). Upregulated genes involve ribosome biogenesis (Rpl6, Rps29, Rpl23a) and immune-related genes (C4b, Il33).[234]

In short, aging OPCs exhibit enriched transcripts linked to mitochondrial dysfunction, inflammasome signaling, dysregulated nutrient sensing, autophagy,

unfolded protein response, and decreased levels of proteins involved in stem cell maintenance, DNA repair, cell cycle control, cholesterol synthesis, and chromatin remodeling. Aging oligodendrocytes show reduced expression of myelin protein genes (Mog, Plp, Cnp) and downregulation of cholesterol synthesis gene (Hmgcs1), as well as upregulated genes involving ribosome biogenesis (Rpl6, Rps29, Rpl23a) and immune-related genes (C4b, Il33).

2.5. Endothelial cells

Cerebrovascular endothelial cells (CECs) are key components of the blood-brain barrier (BBB) and the neurovascular unit. They play a crucial role in regulating molecular transport between the brain parenchyma and the periphery. Senescence in CECs might account for various endothelial dysfunction characteristics observed in aging and cerebrovascular diseases, including blood-brain barrier leakage and neurovascular uncoupling. A SASP in endothelial cells has been noted in age-related conditions like atherosclerosis[235] and the brains of mouse models for premature aging.[236] Yet, human CEC senescence remains poorly defined.

While it's uncertain whether inflammation is the cause or consequence of neurodegenerative processes, it appears to orchestrate and accelerate cellular dysfunctions observed during aging. Natural damage accumulated throughout life probably also contributes to brain injury. Damage in the brain triggers microglia activation, the CNS's first line of defense, leading to rapid recruitment to damage sites for phagocytosis.[237] Astrocyte activation follows, releasing inflammatory mediators that signal back to microglia and may recruit peripheral hematogenous cells. This crosstalk likely benefits the brain by removing injured tissue and defective synapses. However, during aging, chronic stress and accumulating pathology may lead to hyperactivation of glial cells. This hyperactivation increases the release of SASP proteins, including IL-6, TNF-β, TGFβ family ligands, MIF, and YKL-40, all of which are associated with cognitive impairment.[238]

Beyond microglia and astrocytes, BBB maintenance is crucial for normal neuronal function. As the brain ages, normal alterations in BBB permeability occur, impacting the tight control of the neuronal milieu, a critical process involved in the initiation or worsening of cerebrovascular diseases. Elevated proinflammatory factors in the bloodstream disrupt the BBB,[239] leading to increased infiltration of peripheral immune cells and cytokines, which could further stimulate microglia and astrocytes.[240]

Summing up, the BBB, whose key components are endothelial cells, alters permeability during aging.

The effect of human brain aging on various brain cell types is summarized in Fig.2.

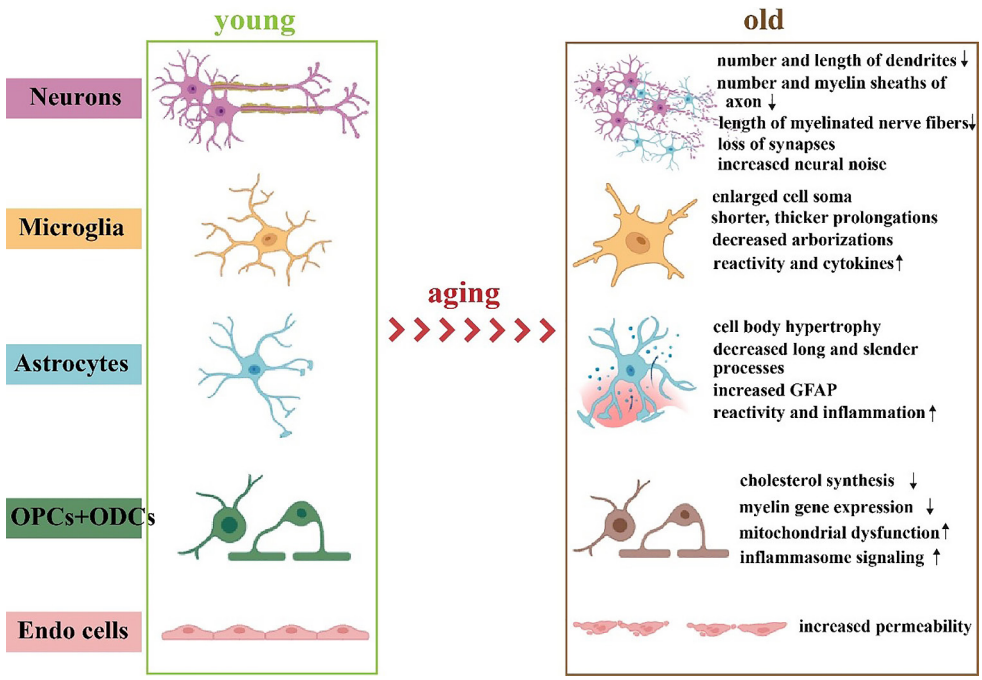

Figure 2. Effects of human brain aging on various brain cell types.

The illustration summarizes the effect of aging on different human brain cell types including neurons, microglia, astrocytes, OPC, oligodendrocytes, and endothelial cells.

CONCLUSION

Aging leads to cortical thinning and volume reduction in the majority of cortical regions. The limbic system experiences aging changes, including cingulate gyrus volume reduction, fornix atrophy, and alterations in the corpus callosum, thalamus, hypothalamus, and amygdala. The basal ganglia and midbrain show aging-related alterations, such as caudate asymmetry, substantia nigra shrinkage, and iron accumulation in the putamen, globus pallidus, pons, and medulla oblongata. Additionally, cerebral blood vessels and meninges change dura mater thinning, arachnoid mater calcification and thickening, and circle of Willis stenosis. With aging, the brain cell types, including neurons, microglia, astrocytes, oligodendrocytes, and endothelial cells alter morphology and function. For instance, neurons undergo morphological changes such as reduced dendrites and dendritic spines, decreased axons with less compacted myelin sheaths, and a significant loss of synapses, and functional changes including mitochondrial dysfunction, oxidative damage, impaired protein homeostasis, dysregulated calcium homeostasis, abnormal DNA repair, and impaired neurogenesis. Meanwhile, most of the glia exhibit reactive morphology and phenotype with increased reactivity and inflammation.

Conflict of Interest Disclosures

The authors have no conflicts of interest to declare.

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Author Contributions

Y.C. and G.Z. drafted the manuscript, B.Z. and Z.B. helped with partial literature search and summary, Q.L. and W.L. revised the manuscript, L.Y. supervised and finalized the manuscript.

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