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The Aging Brain: Structural, Biochemical, Neuropsychological and Genetic Changes

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Abstract

After a brief chronicle of the brain, I explore in this article the various changes (structural, biochemical, neuropsychological, and genetic) that occur during the brain's aging. I also review the brain's markers (epigenetic and others) and the simple, generally accepted measures that can be taken to delay the effects of aging. The two longitudinal studies of aging conducted in the U.S. are summarized in a sidebar.

Abbreviations

ADD: Alzheimer's disease dementia; ALSD: Amyotrophic lateral sclerosis (or Lou Gehrig's disease) dementia; BBB: Blood-brain barrier; CT: Computed tomography; CVDD: Cerebrovascular disease dementia; GABA: Gamma aminobutyric acid; GHEL: Genetics, health, environment, and lifestyle factors; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; NDD: Neurodegenerative diseases; NFT: Neurofibrillary tangles; OS: Oxidative stress; PDD: Parkinson's disease dementia; PET: Positron emission tomography; PHF: Paired helical filaments; RVR: Regional volume reduction; STAC: Scaffolding theory of aging and cognition; TPD: Tau-protein disorders; VTA: Ventral tegmental area.

Keywords

Aging brain; aging delay; aging markers; brain markers; brain plasticity; brain rejuvenation; cognitive deficits; memory changes.

A brief chronicle of the brain

The history of the brain's anatomy, neurology, pathology, and physiology, and the fulcrum of memory can be dated back to humanity's early history in the 17th century BCE in ancient Egypt. It begun with the discovery of the Edwin Smith papyrus, the oldest known treatise on

surgery and trauma. Through the intervening centuries to modern days, that history continues unabated as we still do not truly comprehend the detailed subtleties of the brain's functioning and diseases, as epitomized by the continued lack of cures for neurodegenerative and other brain diseases. This is chronicled in this introductory section that will serve for laying bare the current state of the brain's understanding and research, and particularly of the aging brain.

THE EARLY HISTORY was also marked by Alcmaeon of Croton (5th century BCE), an early Greek medical writer and philosopher-scientist, who considered the brain to be the seat of the mind. Also in Athens, Hippocrates of Kos or Hippocrates II (5th to 4th century BCE), traditionally referred to as the "Father of Medicine" and the writer of the *Hippocratic Corpus* who also coined the *Hippocratic Oath,* greatly advanced the systematic study of clinical medicine. Aristotle (4th century BCE) initially believed the heart to be the seat of intelligence, seeing the brain as a cooling mechanism for the blood.

Herophilus of Chalcedon (335-280 BCE), the "Father of Anatomy" authored detailed works on the brain, eyes, nerves, liver, and arteries that greatly advanced the understanding of both human anatomy and physiology. With Erasistratus of Ceos, he also experimented on living brains.

Herophilus (3rd to 2nd century BCE) advanced the overall knowledge of the structures and functions of the three important organs that were subject to generations of great debate: the liver, the heart, and the brain. In the 2nd century AD, Aelius Galenus (or Claudius Galenus, often Anglicized as Galen or Galen of Pergamon (216 – 129 BCE)), one of the most accomplished of all medical researchers of Antiquity, together with Andreas Vesalius, theorized that the brain functioned by movement of animal spirits through the ventricles.

DURING THE RENAISSANCE, Mondino de Luzzi (or de Liuzzi or de Lucci, also known as Mundinus) (c. 1270 – 1326), wrote the first modern anatomical text (*Anathomia)* that began the modern study of brain anatomy. Niccolò Massa (1485–1569) described the cerebrospinal fluid and discovered that the ventricles were filled with fluid. In the early-to-mid 16th century, Matteo Realdo Colombo (or Realdus Columbus) anatomized the live, active body whereas his contemporaries had anatomized the dead body. His concentration on vivisection enabled him to study the operation of the voice; the motions of the lungs, the heart, and the arteries; the variations of the pulse and other functions; and particularly the dilation and contraction of the brain. For him, the supreme organ was the brain. Andries van Wezel (latinized as Andreas Vesalius) (1514 – 1564), often referred to as the “Founder of modern human anatomy”, wrote *De Humani Corporis Fabrica Libri Septem* (On the fabric of the human body) in seven books, which were considered to be the most influential books on human anatomy and a major advance over the long-dominant work of Galen. The seventh book, in particular, covered the brain and the eyes, with detailed images of the ventricles, the cranial nerves, the pituitary gland, the meninges, the structures of the eye, the vascular supply to the brain and spinal cord, and an image of the peripheral nerves. Thereafter, Jacques Dubois (Latinized as Jacobus Sylvius) (1478 - 1555) first described the venous valves, although their function was later discovered by William Harvey. Although the cerebral aqueduct (Aqueduct of Sylvius) and Sylvian (lateral) sulcus of the brain have been said to be his contributions to anatomy, the aqueduct was described by Galen nearly 1300 years before. Another Sylvius (Franciscus Sylvius, 1614–1672) apparently also described the sulcus which bears his name. The work of Miguel de Villanueva (or Michael Servetus, or Miguel Servet, or Miguel Revés, or else Michel de Villeneuve) (1509 or 1511 - 1553) on the circulation of the blood and his observations on pulmonary circulation were particularly important. Archangelo Piccolomini (or Arcangelo Piccolomini) (1525–1586) was the first to describe and differentiate the white matter of the

cerebrum from the grey matter of the cortex. His observations led to the anatomical study of the cortex by Marcello Malphigi and Antonie van Leeuwenhoek. William Harvey (1578 – 1657) first described completely, and in detail, the systemic circulation and properties of blood being pumped to the brain and the rest of the body by the heart, though earlier writers, such as Realdo Colombo, Michael Servetus, and Jacques Dubois, had provided precursors of the theory.

Further, during the Renaissance period, René Descartes (latinized Renatus Cartesius) (1596 – 1650), often called the "Father of modern philosophy", proposed the theory of dualism to tackle the issue of the brain's relation to the mind. He suggested that the pineal gland was where the mind interacted with the body, serving as the seat of the soul and as the connection through which animal spirits passed from the blood into the brain. This dualism likely provided impetus for later anatomists to further explore the relationship between the anatomical and functional aspects of brain anatomy.

Considered a second pioneer in the study of neurology and brain science, Thomas Willis wrote *Cerebri Anatome* (Latin: Anatomy of the brain) in 1664, followed by *Pathologicae cerebri* (Cerebral pathology) in 1667, itself followed by *Nervosi generis specimen* (Generic nervous specimen). In these, he described the structure of the cerebellum, the ventricles, the cerebral hemispheres, the brainstem, and the cranial nerves. He proposed functions associated with different areas of the brain. The 'circle of Willis 'was named after his investigations into the blood supply of the brain. He was the first to use the word "neurology". Marcello Malpighi (1628 – 1694) also studied the anatomy of the brain and concluded this organ is a gland.

In terms of modern endocrinology, this is a correct deduction because the hypothalamus of the brain has long been recognized for its hormone-secreting capacity. The "Father of Microbiology", Antonie Philips van Leeuwenhoek (1632 – 1723), was among the first to see blood flow in capillaries. Johannes Peter Müller (1801 – 1858) viewed the nerve impulse as a vital function that could not be measured, an idea that was later discarded when his students Emil Heinrich du Bois-Reymond and Hermann von Helmholtz demonstrated the contrary.

Still further during the Renaissance, Marie Jean-Pierre Flourens (1794 – 1867), was the founder of experimental brain science and a pioneer in anesthesia. He pioneered the experimental method of damaging specific parts of animal brains describing the effects on movement and behavior. Pierre Paul Broca (1824 – 1880) is best known for his research on regions of the brain associated with specific functions, in particular language, following work on brain-damaged patients. His work revealed that the brains of patients with aphasia contained lesions in a particular part of the cortex, in the left frontal region. This was the first anatomical proof of localization of brain function. Best known for his research on epilepsy, John Hughlings Jackson (1835 – 1911) described the function of the motor cortex by watching the progression of epileptic seizures through the body. Together with his friends, Sir David Ferrier and Sir James Crichton-Browne, Jackson was one of the founders of the important journal *Brain* (still being published today) dedicated to the interaction between experimental and clinical neurology. Richard Caton (1842 – 1926) was crucial in discovering the electrical nature of the brain by demonstrating electrical impulses in the cerebral hemispheres of rabbits and monkeys. He laid the groundwork for Hans Berger to discover alpha-wave activity in the human brain. Sir David Ferrier (1843 - 1928) conducted experiments on the brains of animals. In 1881, he became the first scientist to be prosecuted under the 1876 Cruelty to Animals Act, which had been enacted following a major public debate over vivisection. Sir William Richard Gowers (1845 – 1915) was described by Macdonald Critchley in 1949 as "probably the greatest clinical neurologist of all time". He is best remembered for his two-volume *Manual of Diseases of the Nervous System* (1886, 1888), affectionately referred to as the Bible of Neurology. Hermann Ludwig

Ferdinand von Helmholtz (1821 – 1894) used a galvanometer to show that electrical impulses passed at measurable speeds along nerves, refuting the view of his teacher Johannes Peter Müller that the nerve impulse was a vital function that could not be measured. The staining method of Camillo Golgi (1843 - 1926) was a major breakthrough in neuroscience. In the 1880s, studies of the brain became more sophisticated with the use of the microscope and the development of the silver staining method of Camillo Golgi that showed the intricate structures of single neurons. This was used by Santiago Ramón y Cajal (1852 – 1934), leading to the formation of the "neuron doctrine", the then revolutionary hypothesis that the neuron is the functional unit of the brain. Cajal used microscopy to uncover many cell types, and proposed functions for the cells he saw. The original investigations of the microscopic structure of the brain by Cajal made him a pioneer of modern neuroscience. For this, Golgi and Cajal are considered as the "Founders of twentieth century neuroscience."

IN THE MODERN PERIOD, the research of Carl (or Karl) Wernicke (1848 – 1905) was influential into the pathological effects of specific forms of encephalopathy and also the study of receptive aphasia (so-called "Wernicke encephalopathy" and "Wernicke's aphasia", respectively). Korbinian Brodmann (1868 - 1918) mapped the cerebral cortex. His work to characterize the brain cytoarchitecture was strongly influenced by Oskar Vogt who postulated that areas with different structures performed different functions, some of which were later associated to nervous functions. Sir Charles Scott Sherrington (1857 – 1952) established many aspects of contemporary neuroscience, including the concept of the spinal reflex as a system involving connected neurons (the "neuron doctrine"), and the ways in which signal transmission between neurons can be potentiated or depotentiated. Sherrington himself coined the word "synapse" to define the connection between two neurons. Harvey Cushing (1869–1939) is recognized as the first proficient brain surgeon in the world. Since the mid-20th century, hundreds of Cajal's drawings illustrating the arborizations ("tree growing") of brain cells are still in use for educational and training purposes. John Farquhar Fulton (1899 - 1960) did comparative studies of the functional localization in the cerebral cortex. His team's findings influenced Egas Moniz who developed the medical practice of the frontal lobotomy in humans. He also founded the Journal of Neurophysiology and published the first comprehensive textbook on the physiology of the nervous system.

Further in the modern period, Margaret Alice Kennard (1899 – 1975) pioneered the field of neuroplasticity when she evidenced the capacity of the brain to re-organize and change with age. She collaborated closely with John Fulton in her famous infant brain studies. Her work led to the creation of the 'Kennard Principle', which posits a negative linear relationship between the age of a brain lesion and the outcome expectancy.

James Wenceslas Papez (1883–1958) described a neural pathway in the brain thought to be involved in the cortical control of emotion (the "Papez circuit"'). Specifically, the hippocampus, the cingulate gyrus ('Broca's callosal lobe'), the hypothalamus, the anterior thalamic nuclei, and the interconnections among these structures constituted a harmonious mechanism that elaborate the functions of emotions. António Caetano de Abreu Freire Egas Moniz, also known as Egas Moniz (1874 – 1955), one of the founders of modern psychosurgery, developed cerebral angiography including the surgical procedure leucotomy—better known today as lobotomy.

Walter Edward Dandy (1886 – 1946), is considered one of the founding "Fathers of neurosurgery", along with Victor Horsley (1857–1916) and Harvey Cushing (1869–1939). He authored numerous neurosurgical discoveries and innovations including the description of the circulation of the cerebrospinal fluid in the brain, the surgical treatment of the hydrocephalus, the invention of air ventriculography and pneumoencephalography, the description of brain endoscopy, the establishment of the

first intensive care unit, and the first clipping of an intracranial aneurysm, which marked the birth of cerebrovascular neurosurgery.

The importance of his numerous contributions to neurosurgery, in particular, and to medicine, in general, has increased as the field of neurosurgery has evolved. By 1950, Sherrington, Papez, and MacLean had identified many of the brainstem and limbic system functions. In the 1950s, David McKenzie Rioch, Francis O. Schmitt, and Stephen Kuffler played critical roles in establishing Neuroscience as a distinct unified academic discipline.

In the mid-to-late 20th century: Stephen William Kuffler (1913 – 1980), often referred to as the "Father of Modern Neuroscience", made numerous seminal contributions to our understanding of vision, neural coding, and the neural implementation of behavior. After this detour into the anatomy, physiology, and pathology of the brain, it is now time to dwell into the several changes taking place in the aging brain.

Changes in the aging brain

Aging of the brain is a process of transformation of the brain in older age. It encompasses changes experienced by all healthy individuals as well as those changes caused by illnesses (including unrecognized illnesses). It is a major risk factor for most common neurodegenerative diseases (NDDs) such as mild cognitive impairment (MCI) and dementias of various types, including: Alzheimer's disease dementia (ADD); cerebrovascular disease dementia (CVDD); Parkinson's disease dementia (PDD); and amyotrophic lateral sclerosis (or Lou Gehrig's disease) dementia (ALSD).

The different functions of the various brain tissues may be more or less susceptible to age-induced changes.

While much research has focused on diseases of aging, there are few informative studies on the molecular biology of the aging brain in the absence of neurodegenerative disease and, likewise, for the neuropsychological profile of healthy older adults. However, research suggests that the aging process is associated with several structural, chemical, and functional changes in the brain as well as a host of neurocognitive changes. In addition, recent reports on model organisms suggest that, as organisms age, there are distinct changes in the expression of genes at the single neuron level. These various changes are discussed below.

Structural changes (9)

Aging entails many physical, biological, chemical, and psychological changes. The brain is no exception to this phenomenon. In 2009, scientists have attempted to map these various changes utilizing conceptual models like the 'scaffolding theory of aging and cognition' (STAC). The STAC model looks at factors like: (a) neural changes to the white matter, (b) cortical thinning, (c) shrinkage, and (d) dopamine depletion. CT scans have found that the cerebral ventricles expand as a function of age. More recent MRI studies have reported age-related regional decreases in cerebral volume. This regional volume reduction (RVR) is not uniform in that some brain regions shrink at a rate of up to 1% per year, whereas others remain relatively stable until the end of the life-span. *Nine* such structural changes are discussed below:

- **Loss of neural circuits and brain plasticity:** Brain plasticity refers to the brain's ability to change structure and function. In animals, one proposed mechanism for the observed deficits in age-related plasticity is the result of age-induced alterations in calcium regulation. Here, the changes in the organism's abilities to handle calcium will ultimately influence neuronal firing and the ability to propagate action potentials that, in turn, would affect the ability

of the brain to alter its structure or function (i.e. its plastic nature). Due to the complexity of the brain, with all of its structures and functions, it is logical to assume that some areas would be more vulnerable to aging than others. Two circuits worth mentioning here are the hippocampal and neocortical circuits. It has been suggested that age-related cognitive decline is due in part not to neuronal death but to synaptic alterations. Evidence in support of this idea from animal work has also suggested that this cognitive deficit is due to functional and biochemical factors such as changes in enzymatic activity, chemical messengers, or gene expression in cortical circuits.

- **Thinning of the cortex and language functions:** Advances in MRI technology have provided the ability to see in vivo the brain structure in great detail in an easy, non-invasive manner. For example, Bartzokis et al., have noted that there is a decrease in grey matter volume between adulthood and old age, whereas white matter volume was found to increase from age 19 to 40, and decline after this age. Studies using voxel-based morphometry have identified areas such as the insula and superior parietal gyri as being especially vulnerable to age-related losses in grey matter of older adults. Sowell et al. (2003) reported that the first six decades of an individual's life were correlated with the most rapid decreases in grey matter density, and this occurred over dorsal, frontal, and parietal lobes on both inter-hemispheric and lateral brain surfaces. It is also worth noting that areas such as the cingulate gyrus, and occipital cortex surrounding the calcarine sulcus appear exempt from this decrease in grey matter density over time. Age effects on grey matter density in the posterior temporal cortex appear more predominantly in the left versus right hemisphere, and were confined to posterior language cortices. Certain language functions such as word retrieval and production were found to be located in more anterior language cortices, and to deteriorate as a function of age. Sowell et al., also reported that these anterior language cortices were found to mature and decline earlier than the more posterior language cortices. It has also been found that the width of sulcus not only increases with age, but also with cognitive decline in the elderly (see Table 1):

	Adulthood	**Older age**
Grey matter Insula; superior parietal gyri	Age 0-60: o Most rapid density decrease: Dorsal, frontal, parietal lobe on both inter-hemispheric and lateral brain surfaces *Note:* Cingulate gyrus and occipital cortex surrounding the calcarine sulcus are exempt from this decrease o More predominant in left vs. right hemisphere and confined to language cortices	o Decrease from adulthood
White matter	o Age 19-40: Increase	o Age > 40: Decrease

Table 1: Age-thinning of the cortex

- **Microstructure and brain volume:** Age-related decrease in grey matter volume is the largest contribution to changes in brain volume. Moreover, neuronal density appears to decrease,

white matter microstructure gets altered, and energy metabolism in the cerebellum gets altered. General cortical atrophy (shrinkage) occurs in aging; for example, the caudate nucleus volume appears to decrease.

- **Neuronal morphology and cognitive deficits:** There is converging evidence from cognitive neuroscientists around the world that age-induced cognitive deficits may not be due to neuronal loss or cell death, but rather may be the result of small region-specific changes to the morphology of neurons. Studies by Duan et al. (2003), have shown that dendritic arbors and dendritic spines of cortical pyramidal neurons decrease in size and/or number in specific regions and layers of human and non-human primate cortex as a result of age. A 46% decrease in spine number and spine density has been reported in humans older than 50 compared with younger individuals. An electron microscopy study in monkeys reported a 50% loss in spines on the apical dendritic tufts of pyramidal cells in prefrontal cortex of old animals (27–32 years old) compared with young ones (6–9 years old).

- **Microtubules destruction and neurofibrillary tangles formation:** Age-related neuropathologies such as AD, PD, diabetes, hypertension and arteriosclerosis make it difficult to distinguish the normal patterns of aging. One of the important differences between normal aging and pathological aging is the location of neurofibrillary tangles (NFT).

  NFT are composed of paired helical filaments (PHF). In normal, non-demented aging, the number of tangles in each affected cell body is relatively low and restricted to the olfactory nucleus, parahippocampal gyrus, amygdala and entorhinal cortex.

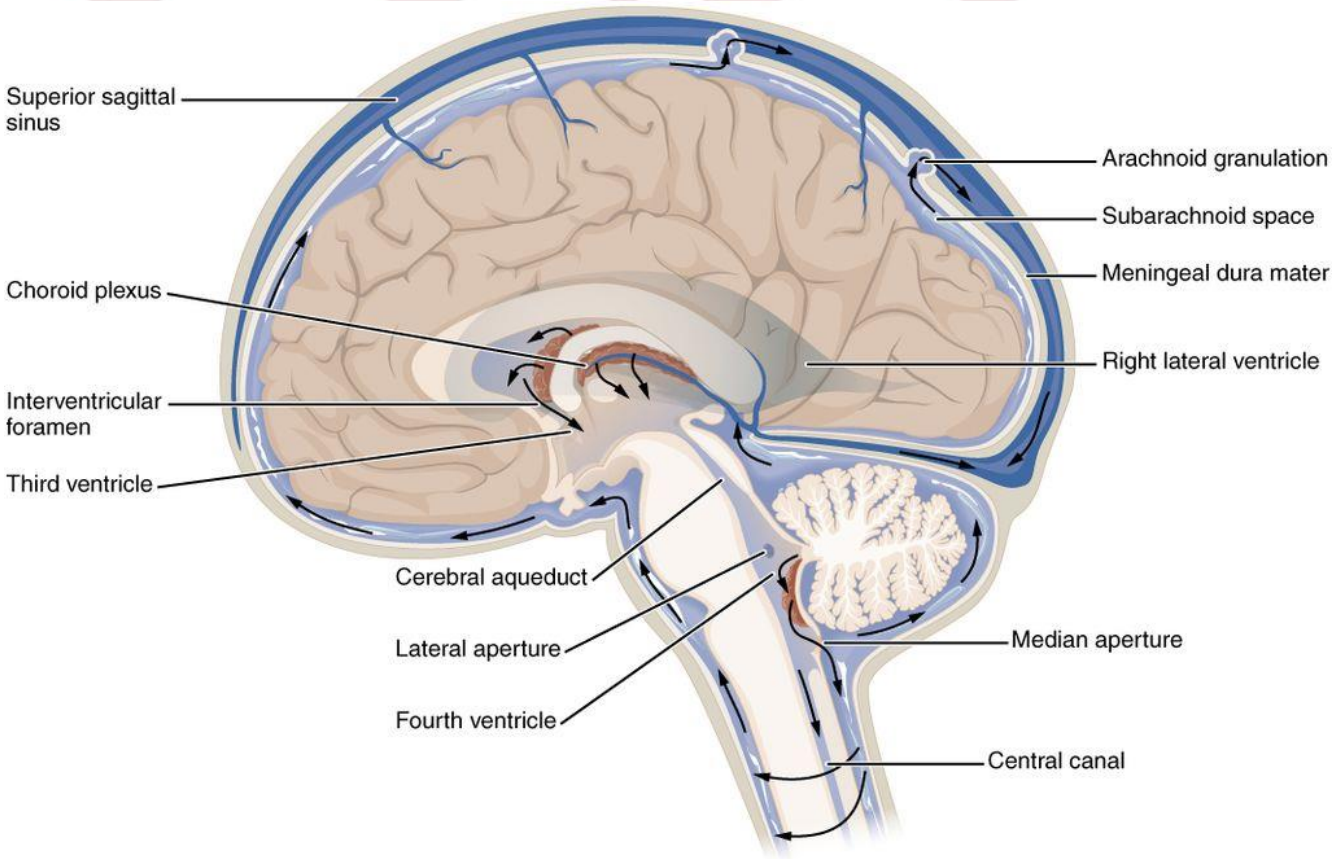
  As the non-demented individual ages, there is a general increase in the density of tangles, but no significant difference in where tangles are found. Tau-protein disorders (TPD) cause microtubule destruction and formation of neurofibrillary tangles. The other main neurodegenerative contributor commonly found in the brain of patients with AD is amyloid plaques. However, unlike tangles, plaques have not been found to be a consistent feature of normal aging.

- **DNA damage and memory and neuronal survival:** At least 25 studies have demonstrated that DNA damage accumulates with age in the mammalian brain. This DNA damage includes: (a) the oxidized nucleoside 8-hydroxydeoxyguanosine (8-OHdG), (b) single-strand breaks, (c) double-strand breaks, (d) DNA-protein cross-links, and (d) malondialdehyde adducts (as reviewed in Bernstein et al.). Increasing DNA damage with age has been reported in the brains of mice, rats, gerbils, rabbits, dogs, and humans. Young 4-day-old rats have about 3,000 single-strand breaks and 156 double-strand breaks per neuron whereas, in rats older than 2 years, the level of damage increases to about 7,400 single-strand breaks and 600 double-strand breaks per neuron. Lu et al. studied the transcriptional profiles of the human frontal cortex of individuals ranging from 26 to 106 years of age. This led to the identification of a set of genes whose expression was altered after age 40. They further found that the promoter sequences of these particular genes accumulated oxidative DNA damage, including 8-OHdG, with age (see DNA damage theory of aging). They concluded that DNA damage may reduce the expression of selectively vulnerable genes involved in

learning and memory and neuronal survival, initiating a pattern of brain aging that starts early in life.

- **Neuroinflammatory changes and aging:** Blood-brain barrier (BBB) permeability, neuroinflammation, neurodegeneration, and gut microbiota-induced systemic chronic inflammation appear to be linked and interacting with aging, e.g. as gut microbiota homeostasis could be disturbed by increasing age. Neuroinflammatory changes, including microglial activation and production of inflammatory cytokines occur with normal aging.

- **Cerebral blood flow and brain rejuvenation:** Cerebral blood flow was shown to decrease 0.3-0.5% per year in healthy aging. An efficiently functioning glymphatic system, involved in waste clearance, may be important for maintaining brain health and its transport efficiency appears to be declining with aging. Factors in the circulation have been shown to modulate aging and to rejuvenate the brain. Figure 1 shows the circulation of the cerebrospinal fluid in the subarachnoid space around the brain and spinal cord, and in the ventricles of the brain (Figure 1).



Reference: OpenStax "Anatomy and Physiology", 2016.
https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface

Figure 1: Circulation of the cerebrospinal fluid

- **Role of oxidative stress and cognitive impairment:** Cognitive impairment has been attributed to oxidative stress (OS), inflammatory reactions, and changes in the cerebral microvasculature. The exact impact of each of these mechanisms in affecting cognitive aging is unknown. OS is the most controllable risk factor. Physiological stress on the body, held to be associated with aging, is caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants. Hence, OS is the damage done to the cells by free radicals that have been released from the oxidation process. Compared to other tissues in the body, the brain is deemed unusually sensitive to oxidative damage. Increased oxidative damage has been associated with NDDs, MCI, and individual differences in cognition in healthy elderly people. In 'normal aging', the brain is undergoing OS in a multitude of ways. The main contributors to OS include: (a) protein oxidation, (b) lipid peroxidation, (c) oxidative modifications in nuclear DNA, and (d) oxidative modifications in mitochondrial DNA. OS can damage DNA replication and inhibit repair through many complex processes, including telomere shortening in DNA components. Each time a somatic cell replicates, the telomeric DNA component shortens. As telomere length is partly inheritable, there are individual differences in the age of onset of cognitive decline.

Biochemical changes (3)

In addition to the structural changes that the brain incurs with age, the aging process also entails a broad range of biochemical changes, most notably changes in three neurotransmitters: Dopamine, serotonine, and glutamate. Specifically, neurons communicate with each other via specialized chemical messengers called neurotransmitters. Several studies have identified a number of these neurotransmitters, as well as their receptors, that exhibit a marked alteration in different regions of the brain as part of the normal aging process. Figure 2 shows the pathways and functions of dopamine and serotonin whereas Figure 3 shows the same for glutamate:

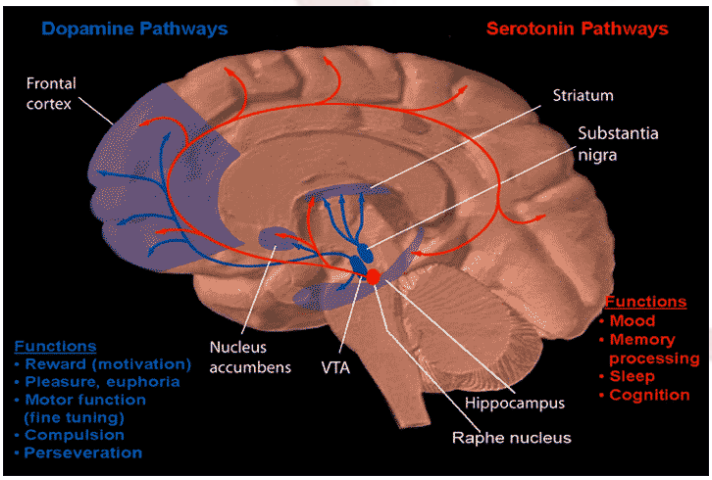


Figure 2: Dopamine and serotonine functions and pathways

Reference: Original: NIDA / Derivative work: Quasihuman - Dopamine Pathways.png
NIH - http://www.drugabuse.gov/pubs/teaching/largegifs/slide-2.gif

- **Dopamine:** In the brain, dopamine plays an important role in the regulation of reward and movement. An overwhelming number of studies have reported age-related changes in dopamine synthesis, binding sites, and number of receptors. Positron emission tomography (PET) in living human subjects have shown a significant age-related decline in dopamine synthesis, notably in the striatum and extrastriatal regions (excluding the midbrain). Significant age-related decreases in dopamine receptors D1, D2, and D3 have been highly reported. A general decrease in D1 and D2 receptors has been shown, more specifically a decrease of D1 and D2 receptor binding in the caudate nucleus and putamen. A general decrease in D1 receptor density has also been shown to occur with age. Significant age-related declines in D2 and D3 dopamine receptors were detected in the anterior cingulate cortex, frontal cortex, lateral temporal cortex, hippocampus, medial temporal cortex, amygdala, medial thalamus, and lateral thalamus. One study also indicated a significant inverse correlation between dopamine binding in the occipital cortex and age. Post-mortem studies also show that the number of D1 and D2 receptors decline with age in both the caudate nucleus and the putamen, although the ratio of these receptors did not show age-related changes.The loss of dopamine with age is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased rigidity. Shown in Figure 2 are the dopamine pathways, offering the following functions: Reward (motivation); pleasure – euphoria, motor functions (fine tuning); compulsion; and perseveration. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus acumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum. By contrast, the functions offered by serotonin are: Mood, memory processing, sleep, and cognition.

Dopamine receptor	Brain regions affected	Effects
D1	o Striatum & extrastriatal regions (excluding midbrain) o Caudate nucleus; putamen	o Significant decline in synthesis o Significant and general decrease in receptors o General decrease in receptor density
D2	o Striatum & extrastriatal regions (excluding midbrain) o Caudate nucleus; putamen; cortex (anterior cingulate; frontal; lateral temporal; medial temporal); hippocampus; amygdala; thalamus (medial; lateral)	o Significant decline in synthesis o Significant and general decrease in receptors
D3	o Striatum & extrastriatal regions (excluding midbrain) o Caudate nucleus; putamen; cortex (anterior cingulate; frontal; lateral temporal; medial temporal); hippocampus; amygdala; thalamus (medial; lateral)	o Significant decline in synthesis o Significant decrease in receptors

Table 2: Age-related decreases in dopamine receptors

Changes in dopamine levels may also cause age-related changes in cognitive flexibility (see Table 2).

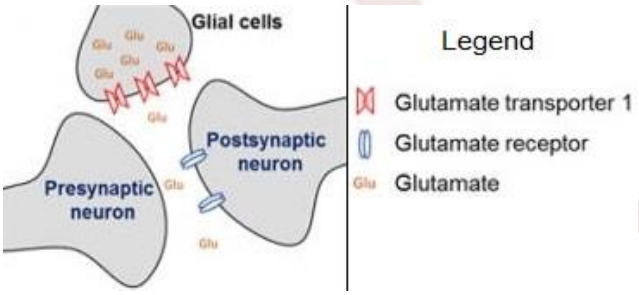
- **Serotonin:** Decreasing levels of different serotonin receptors and the serotonin transporter (5-HTT), have also been shown to occur with age. In vivo studies conducted using PET methods on humans show that levels of the 5-HT2 receptor in the caudate nucleus, putamen, and frontal cerebral cortex, decline with age. A decreased binding capacity of the 5-HT2 receptor in the frontal cortex was also found, as well as a decreased binding capacity of the serotonin transporter (5-HHT) in the thalamus and the midbrain. Post-mortem studies on humans have indicated decreased binding capacities of serotonin and a decrease in the number of S1 receptors in the frontal cortex and hippocampus as well as a decrease in affinity in the putamen.

Table 3 summarizes the age-related decreases in serotonin receptors and transporters.

Serotonin	Brain regions affected	Effects
Receptors (5-HT2)	o Caudate nucleus; putamen; and frontal cerebral cortex	o Decline
S1-receptor	o Frontal cortex; hippocampus	o Decreased binding capacity
Transporters (5-HTT)	o Thalamus; midbrain	o Decline o Decreased binding capacity

Table 3: Age-related decreases in serotonin receptors and transporters

- **Glutamate:** Glutamate is another neurotransmitter that tends to decrease with age. Studies have shown older subjects to have lower glutamate concentration in the motor cortex compared to younger subjects. A significant age-related decline especially in the parietal gray matter, basal ganglia, and to a lesser degree, the frontal white matter, has also been noted. Although these levels were studied in the normal human brain, the parietal and basal ganglia regions are often affected in degenerative brain diseases associated with aging and it has therefore been suggested that brain glutamate may be useful as a marker of aging brain diseases (Figure 3 and Table 4).



Reference: PSS Rao et al. (2015)

Figure 3: Expression of glutamate transporter 1 in glial cells

The image in Figure 3 shows the tissue distribution of excitatory amino acid transporter 2 (EAAT2), a.k.a. glutamate transporter 1 (GLT1), in the brain. The expression of glutamate transporter 1 in glial cells facilitates reuptake of glutamate and decreases extracellular glutamate concentration.

Glutamate	Brain regions affected	Effects
Concentration	o Motor cortex o Parietal grey matter; basal ganglia; and.. to a lesser degree, frontal white matter	o Decrease o Significant decline

Table 4: Age-related decreases in glutamate concentration

Neuropsychological changes (6)

Neuropsychological changes include *six* changes, those in orientation, attention, memory, language, and behavior flexibility as well as qualitative changes, as discussed below:

- **Changes in orientation:** Deficits in orientation are one of the most common symptoms of brain disease, hence tests of orientation are included in almost all medical and neuropsychological evaluations. Research studies have been inconclusive as to whether there is a normal decline in orientation among healthy aging adults. Results have been somewhat inconclusive. However, some studies have suggested that mild changes in orientation may be a normal part of aging and not necessarily a sign of a particular pathology.

- **Changes in attention:** Attention is a broad construct that refers to "the cognitive ability that allows a person to deal with the inherent processing limitations of the human brain by selecting information for further processing". Since the human brain has limited resources, people use their attention to zone-in on specific stimuli and block out others. Many older adults notice a decline in their attentional abilities. If older adults have fewer attentional resources than younger adults, we would expect that when two tasks must be carried out at the same time, older adults' performance will decline more than that of younger adults. However, this hypothesis has not been wholly supported. While some studies have found that older adults have a more difficult time encoding and retrieving information when their attention is divided, other studies have not found meaningful differences from younger adults. Similarly, sustained attention shows no decline with age. There are factors other than true attentional abilities that might relate to difficulty paying attention such as, for example, sensory deficits (impaired hearing or vision) may impact older adults' attentional abilities.

- **Changes in memory:** Many different types of memory have been identified in humans. Memory functions, more specifically those associated with the medial temporal lobe, are especially vulnerable to age-related decline. A multitude of studies utilizing a variety of methods (histological, structural imaging,

functional imaging, and receptor binding) have supplied converging evidence that the frontal lobes and frontal-striatal dopaminergic pathways are especially affected by age-related processes resulting in memory changes.

- **Changes in language:** Behavioral changes associated with age include compromised performance on tasks related to word retrieval, comprehension of sentences with high syntactic and/or working memory demands, and production of such sentences.

- **Changes in behavioral flexibility:** The rapid neurotransmitter GABA (gamma aminobutyric acid)-boosting may be a major potential explanation-component for why learning is often more efficient in children and takes longer or is more difficult with age. Late-stage aging and/or late-life dementias decrease behavioral flexibility and impair deliberation about courses of action.

- **Qualitative changes:** Most research on memory and aging has focused on how older adults perform worse at a particular memory task. However, researchers have also discovered that simply saying that older adults are doing the same thing, only less of it, is not always accurate. In some cases, older adults seem to be using different strategies than younger adults. For example, brain imaging studies have revealed that older adults are more likely to use both hemispheres when completing memory tasks than younger adults. In addition, older adults sometimes show a positivity effect when remembering information, which seems to be a result of the increased focus on regulating emotion seen with age. For instance, eye tracking reveals that older adults showed preferential looking toward happy faces and away from sad faces.

Genetic changes (4)

Variations in the effects of aging among individuals can be attributed to four factors: Genetic, health, environment, and lifestyle factors (acronym GHEL). The search for genetic factors has always been an important aspect in trying to understand neuropathological processes.

Here, research has focused on discovering the genetic component in developing" autosomal dominant" – the pattern of inheritance characteristic of some genetic disorders where "autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes and "dominant" means that a single copy of the mutated gene (from one parent) is enough to cause the disorder. The search for autosomal dominants has greatly contributed to understanding the genetics behind normal or "non-pathological" aging.

The human brain shows a decline in function and a change in gene expression. This modulation in gene expression may be due to oxidative DNA damage at promoter regions in the genome. Genes that are down-regulated over the age of 40 include:

- GluR1 AMPA receptor subunit;
- NMDA R2A receptor subunit (involved in learning);
- Subunits of the GABA-A receptor;
- Genes involved in long-term potentiation e.g. calmodulin 1 and CaM Kinase II alpha;
- Calcium signaling genes;
- Synaptic plasticity genes; and
- Synaptic vesicle release and recycling genes.

Genes that are upregulated include:

• Genes associated with stress response and DNA repair; and

• Antioxidant defense.

Aging markers

Epigenetic age-analysis of brain regions

According to an epigenetic biomarker of tissue age known as 'epigenetic clock', the cerebellum is the youngest brain region (and probably body part) in centenarians. It is about 15 years younger than expected in a centenarian. By contrast, all brain regions and brain cells appear to have roughly the same epigenetic age in subjects who are younger than 80. These findings suggest that the cerebellum is better protected from aging effects, which, in turn, could explain why the cerebellum exhibits fewer neuropathological hallmarks of age-related dementias compared to other brain regions.

Other biomarkers of aging

There is research and development of biomarkers of aging, and detection and software systems to measure the biological age of the brain. For example, a deep-learning software using anatomic MRI estimated brain age with relatively high accuracy, including detecting early signs of AD and varying neuroanatomical patterns of neurological aging.

Delaying the effects of aging

The current state of biomedical technology does not allow to stop and reverse aging. However, one may potentially delay the effects and severity of the symptoms of aging. While there is no consensus of efficacy, the following (unprioritized) *twelve* factors are reported as delaying cognitive decline:

- A number of pharmacological strategies are under investigation, including nicotinamide riboside.
- Maintaining a healthy diet, including omega-3 fatty acids, protective antioxidants (e.g., flavonols-containing foods) as well as potentially anthocyanins- and flavanones-containing ones as in, more generally, Mediterranean diet patterns.
- Caloric restriction and intermittent fasting.
- The microbiome also plays a role. Scientists have shown that transplantation of fecal microbiota from young donor mice into aged recipient mice substantially rejuvenates brain biomarkers of the latter, complementing similar results of a 2020 study. Diet and other factors influence the microbiome. Probiotics such as of L. plantarum may also have relevant effects.
- Physical exercise.
- Limiting stress, having adequate sleep, managing sensory impairments, ceasing smoking, limiting alcohol use.
- Maintaining social and friendship networks.

Cognitive reserve

The ability of an individual to demonstrate no cognitive signs of aging despite an aging brain is called 'cognitive reserve'. This hypothesis suggests that two patients might have the same brain pathology, with one person experiencing noticeable clinical symptoms, while the other continues to function relatively normally.

Studies of cognitive reserve explore the specific biological, genetic, and environmental differences which make some people more resistant to cognitive decline than others.

The sidebar reports on the results of longitudinal studies of aging conducted in the U.S.A.

Conclusions and take-aways

- Aging of the brain is a process of transformation of the brain in older age. It encompasses changes experienced by all healthy individuals as well as those changes caused by illnesses (including unrecognized illnesses). It is a major risk factor for most common neurodegenerative diseases such as mild cognitive impairment and the various types of dementia.

- While much research has focused on diseases of aging, there are few informative studies on the molecular biology of the aging brain in the absence of neurodegenerative disease and likewise for the neuropsychological profile of healthy older adults.

- The aging process is associated with several structural, chemical, and functional changes in the brain as well as a host of neurocognitive changes. In addition, there are distinct changes in the expression of genes at the single neuron level.

- Aging entails many physical, biological, chemical, and psychological changes. The brain is no exception to this phenomenon.

- Structural changes include: Loss of neural circuits and alterations in brain plasticity, thinning of the cortex, decrease in neuronal density, alteration in white matter microstructure, and alteration in energy metabolism in the cerebellum. General cortical atrophy (shrinkage) occurs in the caudate nucleus; general increase in the density of neurofibrillary tangles but no significant difference in where tangles are found; and tau-protein disorders causing microtubule destruction, accumulation of DNA damage, and decrease in the central blood flow without forgetting the role of oxidative stress.

- The aging process additionally entails a broad range of biochemical changes relating to the specialized chemical messengers called neurotransmitters (dopamine, serotonin, and glutamate).

- Neuropsychological changes include changes in orientation, attention, memory, language, and behavioral flexibility.

- The search for genetic factors has always been an important aspect in trying to understand neuropathological processes. The human brain shows a decline in function and a change in gene expression, which may be due to oxidative DNA damage at promoter regions in the genome.

- Measurements of brain changes due to aging include epigenetic age-analysis of brain regions, which suggested that the cerebellum is better protected from aging effects. This, in turn, explains why the cerebellum exhibits fewer neuropathological hallmarks of age-related dementias compared to other brain regions. Other biomarkers of aging are still under development such as detection and software systems to measure the biological age of the brain.

- The current state of biomedical technology does not allow to stop and reverse aging. However, one may potentially delay the effects and severity of the symptoms of aging. While there is no consensus of efficacy, several factors have been reported as delaying cognitive decline.

- Studies of cognitive reserve have explored the specific biological, genetic, and environmental differences which make some people more resistant to cognitive decline than others.

Sidebar – Longitudinal studies of aging

Two important longitudinal studies of aging are being conducted in the U.S. in religious orders establishments. These are summarized below in their main particulars.

1. The Nun Study (1986)

Purpose of the study: "To investigate whether activities, academics, past experiences, and disposition are correlated to continued cognitive, neurological, and physical ability as individuals got older, as well as overall longevity".

Cohort of participants: A group of 678 volunteer American Roman Catholic Sisters who were members of the School Sisters of Notre Dame - a relatively homogeneous group (no drug use, little or no alcohol, similar housing and reproductive histories) to minimize the extraneous variables that may confound other similar research studies.

Inclusion criteria: Be cognitively intact, at least 75 years of age, and participate in the study until time of death, give permission for researchers to have access to their autobiographies and personal documented information, and participate in regular physical and mental examinations.

After-death permission: Permission to donate one's brain for research purposes after death so that it could be neuropathologically evaluated for changes related to Alzheimer's disease (AD) and other dementias.

Consent form: The form agreeing to the terms of the study was willingly signed.

Documents reviewed:

- Personal documents: Autobiographical essays written by the nuns upon joining the sisterhood.

- Convent archives: Researchers accessed the convent archives to review documents amassed throughout the lives of the nuns in the study.

Examinations:

- Annual cognitive and physical function examinations: They were conducted throughout the remainder of the participants' lives. They were designed to test the subject's proficiency with object identification, memory, orientation, and language. These categories were tested through a series of mental state examinations with the data being recorded with each passing test.

- Neuropathology evaluations: They were performed by creating microscope slides from brain autopsy samples and carefully evaluated for AD changes by neuropathologists.

Findings:

- **Education:**

  - Participants who had an education level of a bachelor's degree or higher were less

likely to develop Alzheimer's later in life. They also lived longer than their colleagues who did not have higher education.

- An essay's lack of linguistic density (e.g., complexity, vivacity, fluency) functioned as a significant predictor of its author's risk for developing AD in old age. Roughly 80% of nuns whose writing was measured as lacking in linguistic density went on to develop AD; meanwhile, of those whose writing was not lacking, only 10% later developed the disease.
- Participants' word choice and vocabulary were also correlated to the development of AD.
- Participants writing positively in their personal journals were more likely to live longer than their counterparts.

- **Cognition:** Three indicators of longer life were found: Amount of positive sentences, positive words, and variety of positive emotions used. Less positivity used was associated with greater mortality.

- **Other variables not considered:** Long term hopefulness or bleakness in one's personality, optimism, pessimism, ambition, and others.

- **Lifestyle:** Exercise was inversely correlated with the development of AD, conducing to retaining cognitive abilities during aging. Participants who started exercising later in life were more likely to retain cognitive abilities, even if not having exercised before.

- **Neuropathology:**

  - Tau neurofibrillary tangles located in regions of the brain outside the neocortex and hippocampus: May have less of an effect than amyloid beta plaques located within those same areas.
  - Brain weight: Brains weighing under 1000 grams were seen as higher risk than those in a higher weight class.

- **Age and disease:** Do not always guarantee impaired cognitive ability and that... "traits in early, mid, and late life have strong relationships with the risk of AD, as well as the mental and cognitive disabilities of old age".

- Influence on studies by others:

  - If a person has a stroke, there is a smaller requirement of Alzheimer's brain lesions necessary to diagnose a person with dementia.
  - Post-mortem MRI scans of the hippocampus can help distinguish that some non-demented individuals fit the criteria for AD.
  - There is a relationship between the number of teeth an individual has at death with how likely they were to have had dementia; those with fewer teeth were more likely to have dementia while living.
  - Higher idea density is correlated with better cognition during aging, even if the individual had brain lesions resembling those of AD.
  - Vocation and lifestyle of nuns correlated with higher potential for developing dementia.
  - Correlation between longevity and autonomy. Subjects were shown to have a longer lifespan based on the amount of purposeful and reflective behavior shown in their writing.

The Religious Orders Study follows the earlier Nun Study.

2. The Religious Orders Study (1994)

Purpose of the study: "To explore the effects of aging on the brain".

Cohort of participants: More than 1,000 nuns, priests, and other religious professionals across the United

States.

Findings:

- Cognitive exercise including social activities and learning new skills has a protective effect on brain health and the onset of dementia, while negative psychological factors like anxiety and clinical depression are correlated with cognitive decline.

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