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A Review of Normal Brain Aging: Detailed Study of Physiological Changes, Risk Factors, and Neuroimaging Techniques

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ABSTRACT

Introduction: The process of brain aging is a complex phenomenon that can manifest in a number of ways, including normal, pathological, and accelerated aging, each influenced by modifiable factors such as sex and lifestyle. Subtle, preclinical alterations, including iron accumulation, proteostasis disruption, and inflammation, often precede overt clinical manifestations of cognitive decline, highlighting the need for early detection and intervention.

Material and Methods: This review examines the neuropathological mechanisms of age-related cognitive decline, integrating current knowledge on the interplay of genetic, environmental, and lifestyle factors. Advanced neuroimaging techniques, particularly magnetic resonance imaging (MRI) and positron emission tomography (PET) offer powerful tools for investigating the complex biological and biochemical dynamics of the aging brain. Quantitative Susceptibility Mapping (QSM), a novel MRI technique, provides precise quantification of tissue magnetic susceptibility, enabling detailed assessment of iron deposition and myelin content, both crucial factors in age-related brain changes.

Results: We explore the diagnostic potential of QSM and other advanced neuroimaging techniques for identifying early biomarkers of brain aging and predicting cognitive trajectories. This research indicates that the accumulation of non-heme iron is a primary contributor to neuronal death in brain aging. This conclusion is supported by QSM studies, which have validated the role of iron in this process.

Conclusion: By integrating mechanistic understanding with practical prevention strategies, this research indicates that the accumulation of non-heme iron is a primary contributor to neuronal death in brain aging. Additionally, the literature suggests that dietary and physical activity interventions may beneficially mitigate neurodegeneration associated with aging.

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Introduction

Aging is an inevitable biological process that influences everyone's life. It generally reduces the body's capacity to maintain homeostasis, affecting all organs. Notably, the brain's aging is particularly interesting due to the neurons' incapability for mitosis [1]. Brain aging greatly affects individuals' cognitive and functional activities. It can be divided into three types: Normal Aging, Pathological Aging, and Accelerated Aging. Normal Aging is the least severe and is a universal experience. [2].

Research shows that gender differences can affect how aging manifests and lifestyle changes can influence the visible signs of aging [3, 4]. Furthermore, microscopic alterations, such as iron accumulation or disrupted protein homeostasis, precede macroscopic changes. Consequently, understanding the brain processes during aging is crucial [5, 6].

Neuroimaging techniques, including PET and MRI, significantly help us understand the biological and chemical reactions involved in aging. Progress in these modalities facilitates a more comprehensive understanding of cerebral changes. A notable advancement in MRI is the QSM method, which quantifies tissue magnetic susceptibility at the parts per million level [7, 8].

While numerous significant studies have been conducted, there remains a lack of a comprehensive review that covers all aspects of normal brain aging. This narrative review explores the intriguing effects of aging on the brain, emphasizing its crucial role in cognitive and functional abilities. It provides an overview of physiological and cognitive changes associated with normal aging, the mechanisms and effects of aging, influential risk factors, and diagnostic methodologies for evaluating aging biomarkers. Special emphasis is placed on the advancements in QSM techniques, compiling imaging parameters from

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previous studies to highlight its importance and application in aging research.

Research Design

The search for articles related to aging and neuroimaging was carried out across multiple databases including PubMed, Scopus, Web of Science, and Embase. The Search Strategy (("Quantitative Susceptibility Mapping" OR QSM) AND (Aging OR Ageing OR "Brain Aging" OR "Cognitive Aging" OR "Age-Related Cognitive Decline" OR "Aged" [MeSH Terms] OR "Aging" [MeSH Terms]) AND ("Positron-Emission Tomography" OR PET OR "Tomography, Emission-Computed" [MeSH Terms] OR Iron OR "Iron" [MeSH Terms] OR Brain OR "Brain" [MeSH Terms] OR Neuroimaging OR "Neuroimaging" [MeSH Terms])). The search was limited to articles published from 2015 to 2024.

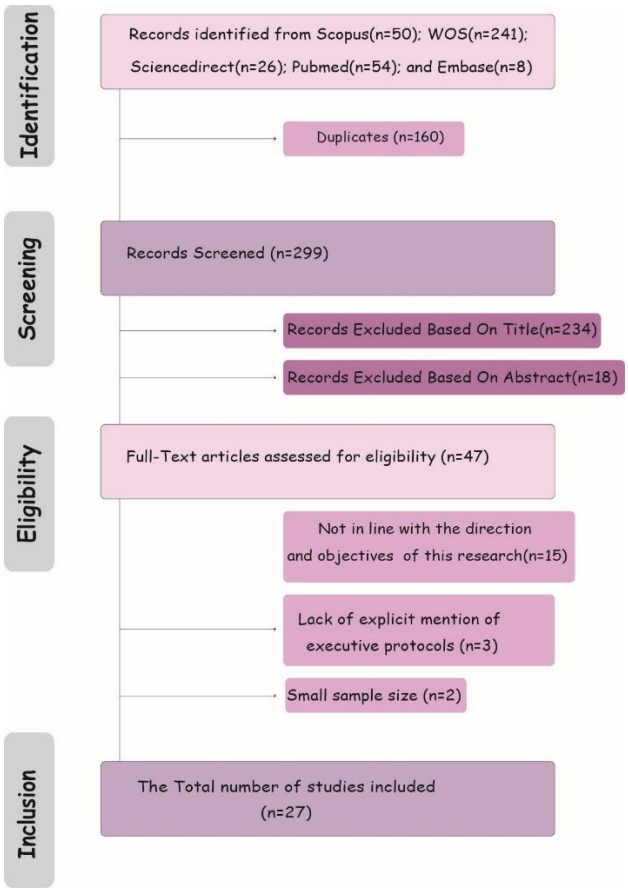

Figure1. Follow-up search method based on PRISMA guidelines

Specifically, the focus was on neuroimaging studies of the aging phenomenon using PET and MRI modalities, original and English language articles, and access to the text of the articles (Figure 1). Studies were included based on the following criteria: (1) human studies and neuroimaging of the aging phenomenon using PET and MRI modalities; (2) availability of full text; and (3) articles in English. Exclusion criteria were: (1) All review articles such as systematic and narrative reviews and case reports (2) Cell, in vitro, and animal studies (3) on patients with other additional pathologies that examined the phenomenon of aging along with other neurological diseases.

Review Findings

Epidemiology

Aging and disability represent critical global health challenges, leading to growing needs for care. The percentage of individuals aged 65 and older exceeds 20% in developed countries and is expected to continue to rise worldwide. This demographic change will be felt on all continents, although it will occur particularly rapidly in developing countries [9]. Notably, disability rates tend to increase with age. In the United States, Medicare data show that the majority of older adult experience one or more disabilities, with prevalence increasing from about 30% in the 65-74 age group to over 75% in the most senior age group, 85 years and older. Additionally, women tend to have higher disability rates than men, and there are differences in disability rates between different racial and ethnic groups, with blacks having higher disability rates compared to whites or Hispanics [10].

Brain and Cognitive Changes During the Aging Phenomenon

As the brain undergoes aging in healthy individuals, it experiences several structural changes that can lead to difficulties in movement execution, the learning of new motor skills, and a decline in cognitive abilities. [11, 12]. Regarding the effects of aging on the cerebellar cortex and white matter (WM), there is limited knowledge about the role of the deep cerebellar nuclei in aging. Early research dating back more than 60 years reported evidence of a reduction in dentate nuclei (DN) volume with age through histological examinations of postmortem brains [13].

These studies found a significant decrease in DN volume in individuals over 70 compared to adults, suggesting an approximately 30% decrease in the elderly. In addition, iron concentrations increase in the DN compared to the surrounding WM tissue and assessments of iron content in the elderly [14-17]. Increased amounts of iron were detected in histological staining of the globose, emboliform, and fastigial nuclei compared to the surrounding tissue [14]. This evolving research provides valuable insights into the aging process of the cerebellum and its nuclei and is a starting point for further research into these critical neurological changes.

Changes in Activities

During the normal aging process, changes in the body can disrupt the way iron is stored, leading to an accumulation of non-heme iron outside of storage areas. This iron buildup can cause oxidative stress [18-20]. Age-related accumulation of non-heme iron in the brain is associated with cognitive and motor performance declines and impairs general cognitive abilities, working memory, and episodic memory [21-24]. Recent research indicates a potential inverse relationship between iron accumulation in

the brain and the functional connectivity of cognitive networks in older individuals [24-26].

However, the connection between brain iron levels and white matter (WM) connectivity, which underpins functional networks, remains underexplored. Age-related increases in non-heme iron may impair WM tracts that support cognitive network interactions. Such disruptions could arise from elevated free iron contributing to demyelination through mechanisms such as altered ion channel functions [27, 28], mitochondrial impairments [28, 29], and oxidative stress damaging oligodendrocytes and myelin [30, 31].

Cognitive Performance

Although the precise mechanisms connecting brain iron and cognitive function are not fully understood, it is suggested that brain iron accumulation may either precede or result from neurodegeneration. Current theories focus on iron's capacity to exacerbate oxidative stress through Fenton's reaction. In this process, ferrous ions react with hydrogen peroxide, creating ferric ions, hydroxide ions, and highly reactive and short-lived toxic reactive oxygen species called hydroxyl radicals [32-34].

With the advancement of MRI-based techniques, scientists can now measure iron levels in the brains of living individuals, particularly as they relate to cognitive function. Research suggests that higher iron levels in the brain are linked to cognitive decline as aging. Studies used MRI to estimate iron levels in the brain have found links between higher iron concentrations and age-related cognitive differences [35].

Longitudinal studies have also shown that increased iron levels in the brain, particularly in the hippocampus, are associated with poorer cognitive performance and accelerated decline in memory and executive functions, even in older adults without cognitive impairment [24, 36, 37].

Additionally, studies have linked higher iron levels in the hippocampus to poorer declarative memory and smaller hippocampal volume in healthy older adults [38]. On the other hand, lower iron levels in the hippocampus and larger volumes in the para-hippocampus have been associated with improved spatial memory over time [39].

Measurement of iron deposition in the hippocampus has been used in clinical studies to identify Alzheimer's disease (AD) patients from healthy individuals through quantitative phase imaging [40] and analysis of ferritin iron accumulation and associated hippocampal tissue damage differentiation [41].

It's important to know that iron is considered a significant source of oxidative stress that contributes to the progression of AD and that defects in iron metabolism in the brain are thought to play a role in the development of Alzheimer's pathology [42].

Morphological Changes

Research has shown that as we age, our brain experiences a decline in primary and higher cognitive functions [43, 44]. This decline is partly due to brain structure changes, even without diseases such as dementia [45-47]. Understanding exactly how and where these structural changes occur in brain aging is critical because it can help us better understand normal brain aging and detect signs of age-related brain diseases [48]. MRI often measures specific brain areas' size, thickness, and physical properties as we age, providing valuable insight into the aging brain [49].

Brain Volume

According to research involving different age groups, brain size increases to a maximum in early adolescence and then declines, with the peak for the parts of the brain that control movement and coordination occurring between the ages of 12 and 14 [50, 51].

The aging process is also associated with neuronal death, which can occur due to many factors. This reduction in neuronal count ultimately leads to brain shrinkage and atrophy, signifying a decrease in brain volume as age advances. This diminution could manifest in the brain's white or gray matter regions. Depending on the areas affected, this could result in various complications, including cognitive impairments, behavioral changes, and motor function abnormalities [51].

White Matter

The relationship between iron accumulation in the brain and WM connectivity, which forms the structural basis for functional connectivity, remains a relatively unexplored area. Excessive non-heme iron accumulation in the brain, often observed with aging, could disrupt WM tracts essential for maintaining cognitive networks. Increased levels of free iron have been shown to induce demyelination through various mechanisms, including altered ion channel activity, impaired mitochondrial function, and oxidative damage to oligodendrocytes and myelin. These processes contribute to the degradation of WM integrity, with potential consequences for cognitive function. Through QSM, studies have observed increased iron accumulation in various brain regions, including the basal ganglia and deep WM, with higher concentrations linked to decreased structural and functional connectivity in the aging brain**.** Specific studies employing QSM have highlighted the potential impact of iron on WM tracts. For instance, research has revealed that increased iron levels in WM regions are associated with reduced WM integrity, as measured by decreased fractional anisotropy (FA) and increased radial diffusivity (RD) in diffusion tensor imaging (DTI) studies [52]. These findings support the hypothesis that iron accumulation contributes to WM degradation, which could underlie age-related cognitive decline.

Studies suggest that the cerebellum and its WM in healthy adults undergo degeneration during aging [53-55]. Imaging studies have revealed a decrease in the volume of the gray and white matter in the cerebellum of older individuals [54, 56]. The anterior lobe of the cerebellum

(lobules I–V) shows a reduction in the number and volume of neuronal cells with age [57, 58]. The posterior lobe of the cerebellum (lobules VI–X) is also affected by aging, although to a lesser extent than the anterior lobe [59].

Grey Matter

The brain's gray matter is composed of various components, among which is the deep gray matter (DGM), which is of significant importance and has been the subject of extensive research. This is primarily due to its crucial role in cognitive functions and memory processes [60].

The DGM nuclei are integral to numerous neural pathways, linking diverse areas of the cerebral cortex [61]. Research has indicated that these DGM structures are implicated in the modulation of physiological behavior [62], memory [36], and cognitive functions [63].

Neurodegenerative diseases such as AD [64], Multiple Sclerosis (MS) [65], and Parkinson's disease (PD) [66, 67] have been linked to pathological changes in the DGM nuclei, including iron accumulation, atrophy, and neuronal degeneration.

Therefore, the quantitative analysis of DGM nuclei throughout an individual's lifespan provides insights into normal brain development and aging and establishes a standard for comparing pathological changes [7, 68]. Most studies of DGM nuclei size in normal aging and development used T1-weighted images with a magnetization-prepared rapid gradient echo (MPRAGE) technique, in which regional volumes were measured using an atlas-based method [50, 68-71]. However, some DGM nuclei are difficult to distinguish from nearby WM in standard T1-weighted images, making their segmentation difficult [72, 73].

Prior research, encompassing both qualitative and quantitative approaches, has demonstrated that quantitative susceptibility mapping (QSM) enhances the accuracy of segmenting DGM nuclei compared to T1-weighted imaging [74-77]. However, studies exploring age-related changes using QSM are limited. A recent multicenter study employing semi-automated segmentation of QSM images revealed that volumes of the caudate nucleus (CN), globus pallidus (GP), putamen (PUT), thalamus, pulvinar thalamus, and red nucleus (RN) tend to decrease with age. Conversely, the volumes of the substantia nigra (SN) and dentate nucleus (DN) were found to increase with age [7].

Pathological Changes

The signs of brain aging are linked to the development of neurodegenerative diseases, which often affect older people, suggesting that neurodegeneration is a more rapid form of brain aging [78].

Some signs of brain aging are present in Normal and pathological aging but are more severe in pathological conditions. These processes include genomic instability, impaired nutrient sensing, degradation of protein homeostasis, and mitochondrial dysfunction. However, normal aging and other neurodegenerative diseases involve several molecular and cellular mechanisms.

Here are the important ones discussed:

Iron Accumulation

The human body contains a higher amount of iron compared to other trace elements. Iron is crucial for various processes in the nervous system, including oxygen transport, neurotransmitter production, DNA synthesis, and myelin formation. The brain must maintain balanced iron levels for normal function, but too much or too little iron can damage nerves differently [34].

As people age, the body's ability to properly store iron is impaired, leading to a buildup of non-heme iron that is not bound to proteins [18, 19, 79]. An increase in cellular iron can also trigger ferroptosis, a form of cell death mediated by iron. This occurs when lipid peroxidation, dependent on iron, reaches exceptionally high levels, instigating an innate immune response. This leads to tissue damage, increased iron levels due to cellular iron release, increased lipid peroxidation, and mitochondrial dysfunction [33, 80].

In neurodegenerative disorders, iron accumulation has been detected within protein aggregates, including amyloid beta and tau. Laboratory studies suggest that iron may promote the aggregation of amyloid beta and enhance its neurotoxic effects [32, 81]. These mechanisms could ultimately contribute to neuronal loss, disrupting regional brain function and leading to changes in cognitive performance.

This excess of non-heme iron can lead to the formation of reactive oxygen species (ROS) [82, 83], which can damage the cells of the nervous system (e.g., lipids, proteins, and nucleic acids), affects neurons, glia and myelin, and impairs cognition [19, 79, 82, 84]. For example, high levels of non-heme iron in the brain have been linked to poorer working memory performance and worsening of other cognitive and motor functions [24, 31, 36, 85, 86]. Figure 2 adapted from the article "Implication of Ferroptosis in Aging" [87] which represents iron dysregulation.

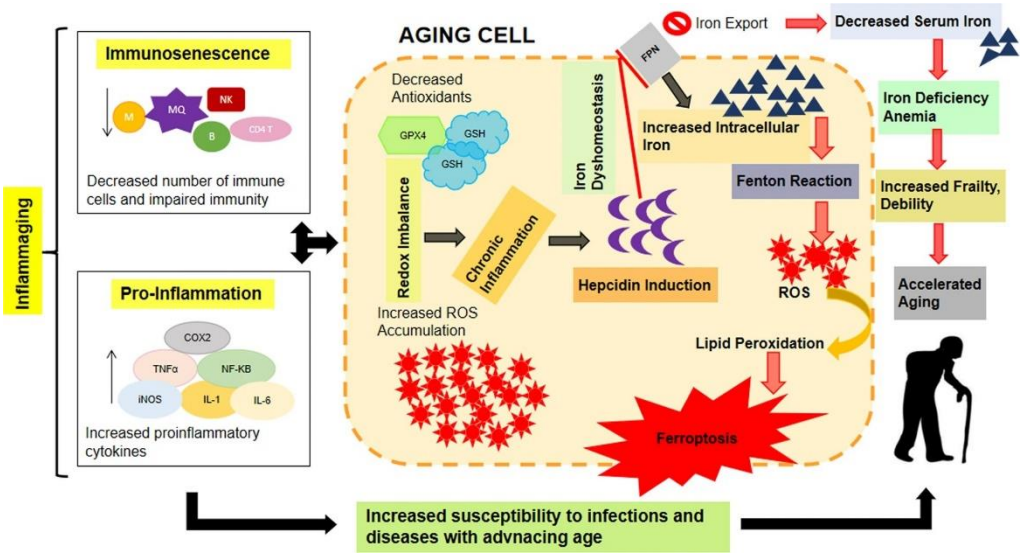

Figure 2. Adapted from the article "Implication of Ferroptosis in Aging" on Nature

The decline in immunity and redox balance with age leads to chronic inflammation and increased hepcidin production, causing iron homeostasis disruption and ferroptosis. This contributes to accelerated aging and associated frailty and debility.

Apolipoprotein E (apoE)

Fat metabolism and cholesterol regulation in the central nervous system (CNS) are mediated by apolipoprotein E (apoE), an essential protein. The most common genetic risk factor for AD, a brain disorder, is the apolipoprotein E ε4 allele (APOE4) [88, 89].

People who carry the APOE-ε4 allele in their genes are more likely to experience cognitive decline and develop AD pathology [90, 91].

Impaired Protein Homeostasis

The ability of protein chaperones and proteolytic systems to prevent protein aggregation decreases with age [92]. When these systems are overwhelmed by the number of proteins that need to be folded or broken down, some proteins form insoluble aggregates. This can happen more quickly in stressful situations, such as mutations in the genes that code for proteins prone to aggregation [93].

In many age-related neurodegenerative diseases, loss of protein homeostasis is more severe and causes more damage. For example, AD is characterized by the accumulation of Aβ and the abnormal phosphorylation of Tau, and PD is characterized by the presence of α-synuclein aggregates in the dopamine-producing neurons [94].

Glucose Metabolism

Numerous brain regions, including the temporal and parietal lobes and the motor cortex, display reduced glucose metabolism in aging brains [95]. This reduction is more pronounced in older individuals with dementia [96]. In neurodegenerative conditions such as AD and PD, the brain's capacity to utilize glucose and generate energy is associated with the activity of signaling pathways, including IIS, mTOR, and AMPK. Studies indicate that insulin resistance in the brain may hasten aging processes, whereas preserving insulin sensitivity in the brain could mitigate age-related decline [97].

Risk Factors Associated with Brain Aging Phenomenon

Aging is not the same for everyone; therefore, a person's age does not always tell us how likely they are to face age-related problems. People have different genes and environments that influence how their cells and tissues age [98]. Based on the studies, the most relevant risk factors for aging are defined as follows.

Sex

A person's gender influences how iron content and volume change with age in DGM structures under the cortex. Various MRI methods show that men have more iron in these structures than women [31, 99]. Men also exhibit more significant fluctuations in iron levels with age, especially in the RN, PUT, and pulvinar [100]. A study that examined brain tissue samples found that women ages 50 to 90 had less brain iron than men [16]. In women, the volume of DGM structures was smaller than in men when adjusted for brain size [99], while in men aged 19 to 86 years, there was a more rapid decrease in volume in the right PUT, right GP, and right thalamus occurred [51]. Amygdala growth slowed later and more slowly in men than women, but men reached maximum amygdala volume slightly earlier than women (21 years versus 25 years) [101].

Diet

Determining what factors can help prevent iron accumulation in the brain is essential, as this is linked to age and cognitive decline. Previous animal studies have

shown that some nutrients, such as vitamins, polyunsaturated fatty acids (PUFA), flavonoids, and iron chelators, can protect the brain from the harmful effects of too much iron on cognition. These nutrients have antioxidant, anti-inflammatory, and iron-lowering properties and may prevent or reduce ferroptosis, a form of cell death caused by iron [102-106]. Likewise, many studies have shown a positive relationship between the consumption of these nutrients and cognitive function [107-110]. Too much alcohol can increase ferritin levels in the blood, which can damage tissues, including the liver and brain [111].

Physical Activity

Physical inactivity was one of the main risk factors. Physical activity (PA) has a positive impact on cognitive performance and brain aging outcomes [112] and reduces the risk of developing dementia, such as AD [113]. Therefore, PA is recommended as a lifestyle change for older adults [114]. However, the precise biological mechanisms linking PA and exercise to brain health are still being investigated. To make accurate PA suggestions and find new treatment targets based on risk level, it is crucial to identify and understand these biological mechanisms well [115]. The brain is very susceptible to oxidative stress due to its high metabolic activity, the number of substances that can be oxidized, and its low antioxidant defenses [116]. PA, on the other hand, is associated with less oxidative stress, better WM integrity, and higher myelin content [117]. Regular PA can improve the ability of cells and tissues to resist oxidative stress and increase blood flow and growth factors in the brain, which are related to the maintenance of neurons and improving memory and brain plasticity [118]. By increasing the activity of enzymes that act as antioxidants, PA may help prevent or reduce diseases caused by oxidative stress, such as heart and brain diseases such as AD and PD [119].

In addition to the mentioned factors, to enrich the discussion on brain aging, it's essential to consider how systemic factors like genetics, chronic inflammation, hormonal shifts, sleep quality, stress, and cardiovascular health contribute to neurodegeneration. Each of these elements plays a significant role in the biological processes underlying brain aging, influencing aspects like neuroinflammation, metabolic stability, and the integrity of brain structures.

Genetics: Genetic predispositions can affect susceptibility to age-related brain changes. For example, variants in the APOE gene are linked to AD, influencing both lipid metabolism and amyloid-beta accumulation [90, 91], which contributes to neurodegenerative processes. Genes associated with iron metabolism, such as HFE, also play a role, as disruptions can lead to increased iron accumulation, exacerbating oxidative stress and tissue damage in the brain [120].

Inflammation: Aging is frequently accompanied by chronic, low-grade inflammation, often termed "inflammaging." This inflammatory state can damage neurons and disrupt the blood-brain barrier, facilitating further neuroinflammation and cognitive decline. Microglial activation, a response to inflammation that can be measured with PET tracers like TSPO, reflects the role of the immune system in aging brains [121].

Hormonal Shifts: Hormones such as estrogen and testosterone influence neuroplasticity, synaptic density, and blood flow in the brain. Age-related hormonal declines are linked to cognitive changes, as observed in post-menopausal women with decreased estrogen, potentially increasing their risk of neurodegenerative diseases [122].

Sleep Quality: Poor sleep is associated with increased amyloid-beta and tau accumulation in the brain, contributing to memory issues and dementia risk. Sleep disturbances also affect hemodynamic processes, impairing the clearance of neurotoxic waste products, which accelerates aging in brain structures [123].

Stress: Chronic stress can lead to increased cortisol levels, which have been associated with hippocampal atrophy and memory deficits. Excessive cortisol can alter neuroplasticity and exacerbate oxidative stress, increasing the risk of neurodegeneration [87].

Cardiovascular Health: Hemodynamic factors such as blood pressure significantly impact brain aging. Hypertension, for example, is associated with microvascular damage in the brain, increasing the risk of cognitive decline and dementia. Reduced blood flow and oxygen supply due to cardiovascular diseases can also lead to WM damage, particularly detectable through DTI and QSM techniques, as these imaging methods reveal disruptions in WM tracts and iron accumulation related to vascular insufficiency [124].

Hemodynamic Parameters and Brain Aging: Blood hemodynamic factors influence cerebral blood flow, impacting brain structure and function. Increased blood pressure can contribute to small vessel disease, which reduces oxygen and nutrient delivery, impairing brain function over time [124, 125]. Chronic hypertension is linked to WM hyperintensities and gray matter atrophy, which can be observed using MRI and DTI, while QSM can highlight iron accumulation associated with vascular changes.

Diagnostic Methods of Brain Aging

Brain aging is the gradual decline in brain structure and function over time. It can affect cognitive abilities, memory, and mental health. There are various methods and tools to diagnose brain aging, such as medical history, cognitive testing, blood tests, cerebrospinal fluid analysis, brain scans, biomarkers, and machine learning algorithms. These methods and tools can help physicians and researchers assess the biological age of the brain, identify the risk factors and causes of brain aging, and develop preventive and therapeutic interventions.

Clinical Symptoms, Blood, and Genetic Markers

Aging affects every person differently. Therefore, various methods have been developed to measure

biological age, indicating health status better than chronological age. One of the main problems associated with aging is brain shrinkage, which leads to cognitive decline and affects the individual's quality of life. It is also a common feature of neurodegenerative diseases such as AD and PD [126, 127]. Structural and functional MRI (fMRI) can reveal the aging process in different brain regions. A biomarker of aging is delta age, which represents the difference between actual chronological age and age predicted based on MRI features [128]. By estimating delta age, researchers have found genetic and clinical factors significantly associated with it. These factors include bone mineral density, blood pressure, and type 2 diabetes [129]. Some of the genes linked to delta age are KANSL1, MAPT-AS1, CRHR1, NSF on chromosome 17, KLF3 on chromosome 4, RUNX2 on chromosome 6, and NKX6-2 on chromosome 10 [130, 131]. When cognitive test results are also considered, SNPs in the MED8, COLEC10, and PLIN4 genes are associated with delta age [132].

Advance Neuroimaging Methods

Brain functions can be examined through neuroimaging. This is a way to see the brain's structure and activity without opening the skull [133, 134]. Neuroimaging can help us learn how different parts of the brain work together to carry out various cognitive and behavioral processes, such as recognizing, focusing, remembering, speaking, selecting, and controlling emotions [135]. Some standard neuroimaging methods used in cognitive neuroscience research are fMRI, PET, DTI, EEG, and magnetoencephalography (MEG) [136-138].

Positron Emission Tomography

PET measures changes in brain metabolism and can provide information about the brain's neurochemical activity. Four PET methodologies can be employed to identify age-related iron deposition: Amyloid PET, Tau PET, TSPO PET, and FDG PET. Among these, the TSPO PET method remains relatively unexplored [139].

[18F]-Fluorodeoxyglucose (FDG), the most prevalent radiotracer employed in PET, indirectly indicates neuronal function and integrity by evaluating glucose metabolism. Clinically, unique spatial patterns of diminished glucose metabolism, as observed on FDG-PET, are utilized to distinguish AD from other forms of dementia [140].

Presently, the primary method for in vivo PET imaging of microglial activation, particularly during neuroinflammation, involves targeting the 18-kDa translocator protein (TSPO) located in the outer membrane of the mitochondria. Given the low baseline expression of TSPO in the central nervous system, any increase in the TSPO-PET signal within the brain indicates an upregulation in activated microglia. This data can be integrated with information derived from separate amyloid- and tau-PET studies conducted on the same patients [141].

Amyloid PET is extensively employed in both research and clinical trials as a tool for evaluating pathological alterations associated with AD. It furnishes information on a regional scale about the existence of amyloid in the brain [142, 143]. Tau, the other principal pathological protein of AD, accumulates in the brain in the form of neurofibrillary tangles. This accumulation correlates robustly with neurodegeneration and cognitive deterioration [144, 145]. To detect β-amyloid and tau-protein in the gray matter of the brain, PET imaging using Pittsburg compound (PiB) and flortaucipir (FTP), respectively, is the most reliable method [146]. However, PET imaging has disadvantages, such as low spatial resolution, radiation exposure, and binding to molecules other than the target molecules [64].

Magnetic Resonance Imaging

The brain undergoes various structural changes as we age, many of which can be observed using MRI. Regarding its superior contrast resolution compared to other modalities, MRI emerges as an optimal choice for the structural and functional exploration of the brain, facilitated by fMRI. Furthermore, the sensitivity of MRI to iron properties renders it a suitable candidate for quantitative imaging, thereby enabling the investigation of iron in the brain [147]. To measure changes in iron levels in the brain without Invasive procedures, MRI with T2* and susceptibility-weighted imaging is often used [147, 148]. A standard MRI method for quantitative studies uses 3D multi-echo gradient recalled echo (GRE) imaging techniques to acquire whole brain R2* data and quantitative susceptibility mapping data [7].

Quantitative Susceptibility Mapping

Quantitative Susceptibility Mapping is a sophisticated method that enables the quantification and measurement of the magnetic susceptibility of tissues. One of the primary contributors to cerebral aging is the accumulation of non-heme iron. Given that iron in its biological form exhibits paramagnetic properties, it is feasible to locate regions of iron accumulation utilizing the QSM technique. This capability highlights the potential of QSM as a valuable tool in studying brain aging processes.

This technique incorporates both magnitude and phase images. The magnetic susceptibility effect is extrapolated from the phase image, while the magnitude image facilitates the creation of the brain tissue mask[149]. The susceptibility data, extracted from the phase image, is subjected to several processes, including phase unwrapping and background field removal, utilizing specific tools (Figure 3). This data is procured via Multi-Echo GRE sequences, which are sensitive to changes in brain susceptibility[150]. This highlights the comprehensive nature of this technique in capturing and analyzing susceptibility changes.

R2* is influenced by water, iron, and field strength, while QSM does not depend on water content, echo time, or field strength. QSM is a helpful method for measuring iron content along with R2* [151, 152]. QSM is a reliable and accurate method of measuring iron levels in the brain without surgery [153, 154]. It is often used to measure the changes in magnetic susceptibility of iron and myelin in the brain [8, 155, 156].

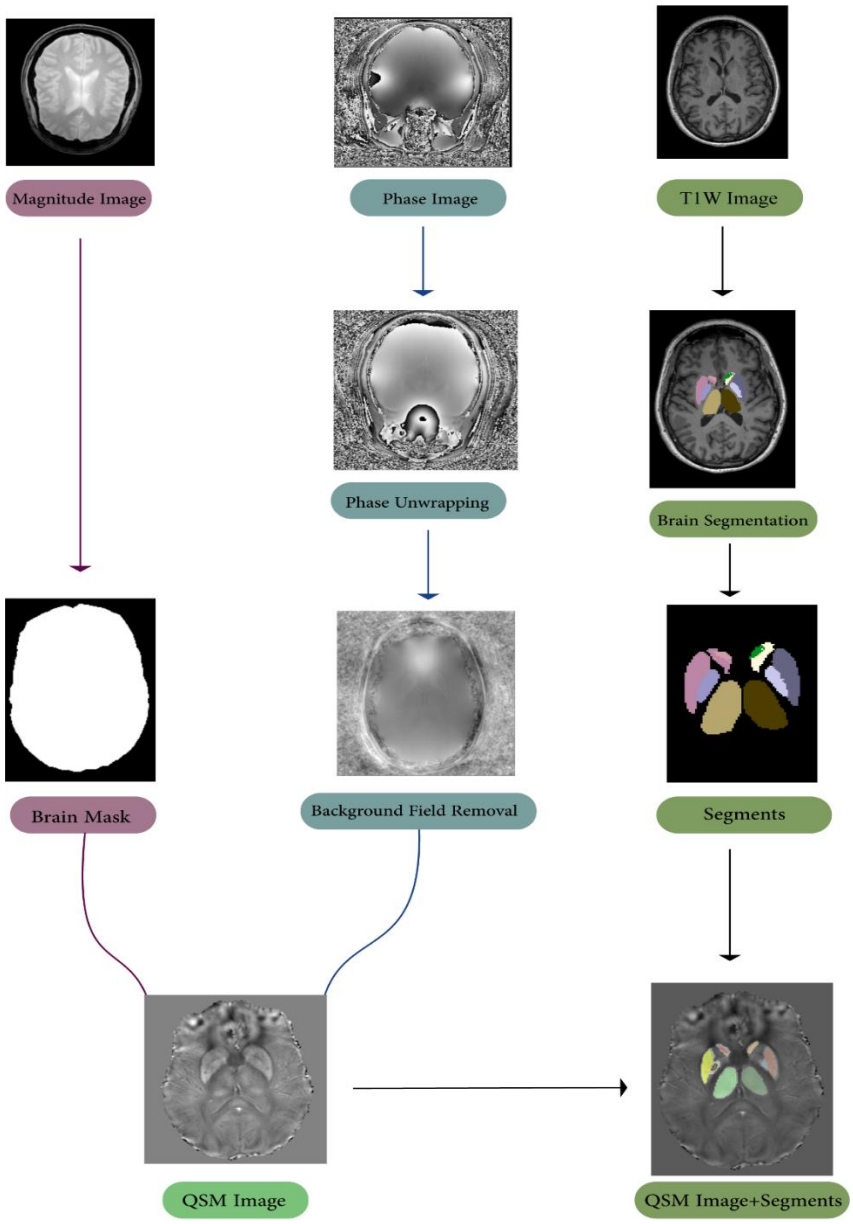

Figure 3. QSM image reconstruction steps. In order to reconstruct the QSM, T1-weighted images, phase, and magnitude images of the GRE multi-echo sequence are needed. At first, the brain mask is extracted from the magnitude images. Two operations, Phase unwrapping, and background field removal, are applied to the phase images, and QSM reconstruction is performed by merging the brain mask and the processed image. The desired areas are segmented on T1-weighted images, and with the help of these segments, quantitative values related to iron deposition in QSM images are determined[157].

For example, previous studies have shown that iron levels are not the same in different brain parts, and the basal ganglia contain the most iron. They have also shown that myelin grows during brain development and shrinks in WM diseases [158]. QSM has proven to be an excellent way to observe the changes in iron and myelin over time during normal brain development [159, 160].

QSM helps study the deep-brain nuclei, which contain much iron and do not have blooming artifacts that distort the image [161]. Previous QSM studies have found a strong association between age and susceptibility in the head of the CN, PUT, GP, RN, SN, and pulvinar thalamus [100, 162-165].

Recent Advances in Understanding Brain Changes during Normal Aging Using QSM

Recent studies have increasingly utilized QSM to investigate brain changes associated with normal aging. These studies have provided valuable insights into the alterations in brain iron levels, myelin content, and other tissue properties as individuals age. The findings from these investigations are detailed in the subsequent sections, where we critically analyze and discuss the implications of these changes for our understanding of the aging brain (Table 1).

Table 1. Quantitative Susceptibility Mapping (QSM) Studies A comprehensive summary of methodological details and key findings from various investigations

Author/year	Subjects	Modality and Sequence	Imaging parameters	Software and Analysis	Results
Manju Liu 2016 [165]	174 healthy adults, aged 20–69 years	MRI, 1.5T GE scanner, 3D GRE sequence for QSM	TR/TE = 53/40 ms, flip angle = 20°, slice thickness = 3 mm, 40 slices, bandwidth = 122 Hz/pixel, FOV = 24 cm, matrix = 384 × 320, in-plane resolution = 0.60 × 0.75 mm	In-house MATLAB-based SMART 2.0 toolbox (MRI Institute, Detroit, MI). Steps: brain extraction (BET), phase unwrapping (3D-SRNCP), background field removal (SHARP), iterative QSM reconstruction	Highest iron levels in GP, followed by SN, RN, PUT, CN, pallidum, and thalamus. Significant susceptibility differences between hemispheres across all age groups.
Ninni Persson 2015 [100]	183 healthy adults, aged 20–69 years	MRI, 1.5T GE Signa EXCITE, 3D flow-compensated GRE sequence for QSM	True axial plane, TE = 40 ms, TR = 53 ms, flip angle = 20°, slice thickness = 3 mm, bandwidth = ±31.25 Hz/pixel, FOV = 24 cm, matrix = 512 × 512 × 40, SENSE factor 2, scan time = 6 min 28 s	Modified MEDI algorithm for QSM reconstruction, bypassing phase unwrapping and skull stripping, with integrated background field removal	GP showed highest susceptibility; thalamus lowest. Susceptibility increased linearly with age in striatum. Women had lower SN susceptibility after age adjustment; men showed linear susceptibility increase in pulvinar with age, while women's pulvinar susceptibility plateaued from midlife. Postmenopausal women (51+) had lower subcortical gray matter susceptibility.
Yan Li 2020 [7]	623 healthy adults, aged 20–90 years	MRI, multi-site (GE HDX 1.5T, Philips Ingenia 3.0T, Siemens Prisma 3.0T)	TR = 53/25/25 ms, TE = 40/17.5/17.5 ms, voxel sizes = 0.6 × 0.75 × 3 mm (1.35 mm^3), 0.67 × 1.34 × 2 mm (1.80 mm^3)	SMART 2.0 MATLAB toolbox; brain extraction (BET), phase unwrapping (3DSRNCP), background field removal (SHARP), susceptibility map reconstruction via iterative TKD (threshold = 0.1)	Positive age correlation for CN, PUT, RN, SN, DN ($p < 0.001$). Thalamus showed strong negative correlation ($p < 0.001$). GP had a non-significant negative slope ($p = 0.49$); pallidum had a small but significant negative slope ($p < 0.01$).
Romana Burgetova 2021 [162]	95 healthy adults, aged 21–58 years	MRI, Siemens Skyra 3T, 3D flow-compensated multi-echo GRE	TR = 33 ms, first TE = 4.5 ms, echo spacing = 5 ms, last TE = 29.5 ms, 6 echoes, flip angle = 18°, FOV = 195 × 240 × 164 mm, resolution = 0.94 × 0.94 × 0.94 mm^3	QSM processed via multi-scale dipole inversion in QSMbox software. (https://gitlab.com/acostaj/QSMbox)	Significant linear susceptibility increases in RN ($\beta = 1.30$, $p < 0.001$), PUT ($\beta = 0.89$, $p < 0.001$), SN ($\beta = 0.76$, $p < 0.001$), DN ($\beta = 0.73$, $p = 0.002$), external GP ($\beta = 0.62$, $p < 0.001$), CN ($\beta = 0.46$, $p < 0.001$), subthalamic nucleus ($\beta = 0.43$, $p = 0.024$). Internal GP showed no significant age effect ($\beta = 0.20$, $p = 0.15$). Thalamus susceptibility peaked at age 40, then declined.
Valentino Zachariou 2022 [52]	95 healthy adults, aged 60–86 years	MRI, Siemens 3T Prisma, 3D multi-echo GRE	Sagittal 3D spoiled GRE, 8 echoes, TR/TE1/ΔTE = 24 ms/2.98 ms/2.53 ms, flip angle = 15°	QSM maps generated using validated Ironsmith software	Increased iron levels linked to reduced neurite density in task-relevant WM networks. Increased cortical iron correlated with lower neurite density in adjacent WM tracts, suggesting iron accumulation disrupts WM tracts critical for cognition in aging.
Sarah Treit 2021 [166]	498 healthy individuals, aged 5–90 years	MRI, Siemens 3T Prisma, axial-oblique 3D multi-GRE	TE1 = 3.82 ms, echo spacing = 5.49 ms, FOV = 240 × 202 mm^2, resolution = 0.94	QSM processing: RF offset correction, best-path phase unwrapping, magnitude-weighted	Susceptibility followed cubic trends: increases with age in CN, PUT, GP; thalamus showed increase in

			× 0.94 mm², bandwidth = 260 Hz/pixel, 2× parallel imaging	least squares field map fitting, brain masking (FSL BET), V-SHARP background field removal, nonlinear MEDI for susceptibility maps	childhood, plateau in mid-adulthood, and decrease in later years.
Gaiying Li 2023 [4]	220 healthy adults, aged 10–70 years	MRI, Siemens Magnetom Trio Tim 3T, 3D spoiled multi-echo GRE	TR = 60 ms, TE1 = 6.8 ms, ΔTE = 6.8 ms, 8 echoes, flip angle = 15°, FOV = 240 × 180 mm², resolution = 0.625 × 0.625 mm², slice thickness = 2 mm, 96 slices	QSM reconstructed using MEDI toolbox	Assessed CN, GP, PUT, RN, SN, DN. Mean susceptibility increased with age in all regions. Strongest quadratic relationships in PUT ($R^2 = 0.401$, $p < 0.001$), CN ($R^2 = 0.327$, $p < 0.001$), GP ($R^2 = 0.211$, $p < 0.001$).
Guevara et.al 2024 [167]	77 healthy adults, aged 54–78 years	MRI, Siemens 7T Magnetom, 3D multi-echo GRE	Acquisition time = 9:48 min, FOV = 256 mm, voxel size = 0.8 mm³ isotropic, TR = 37 ms, TE = 1.68 ms, ΔTE = 3.05 ms, 10 echoes, flip angle = 30°	QSM maps computed via Python pipeline using Common Workflow Language	Higher iron deposition in CN and PUT in older subjects. Females showed higher iron in amygdala; males in thalamus. Females had differences in accumbens, CN, hippocampus for age-sex effects. Higher cardiovascular risk linked to increased iron without cognitive impairment.

Discussion

The increasing growth of the elderly population is a global concern, as older individuals often require more care due to decreased mobility and cognitive decline. These reductions in abilities are mainly attributed to brain aging. Therefore, studying brain aging is essential, but the microscopic changes and risk factors associated with this type of aging are not well-defined.

Research indicates that as people age, the number of neurons in their brains decreases. The location of neuronal death directly affects specific abilities. For instance, a reduction in neurons in the motor cortex can lead to movement impairments. Neuronal death in most DGM nuclei can affect cognitive abilities and memory in individuals experiencing this process. When brain neurons begin to deteriorate, the size of brain regions diminishes, leading to brain atrophy. This stage is often considered too late to prevent aging-related issues. Therefore, understanding the causes of neuronal death in the brain is crucial to mitigate its consequences or slow down aging.

Multiple processes precipitate neuronal death. One significant factor is the excessive accumulation of non-heme iron in the brain, which generates Reactive Oxygen Species, causing oxidative stress and neuronal death. Another process involves impaired protein homeostasis, characterized by a decreased ability to prevent protein aggregation. Specific protein aggregations exacerbate many age-related neurodegenerative diseases. An additional factor contributing to neuronal death is impaired glucose metabolism. Numerous brain regions, particularly the temporal and parietal lobes and the motor cortex, exhibit reduced glucose metabolism in older brains, leading to neuronal death. Furthermore, the presence of the APOE-ε4 allele renders individuals susceptible to neuronal death and the onset of neurodegenerative diseases.

As mentioned earlier, a key finding indicates that neuronal death, instigated by oxidative stress, is mainly due to the excessive iron accumulation in the neurons. Various neuroimaging modalities are mentioned, and in comparison, PET excels at revealing molecular markers like amyloid and tau deposits, which are directly relevant to Alzheimer's pathology. QSM complements PET by providing direct, non-invasive iron quantification, a significant factor in aging and neurodegeneration. DTI does not measure molecular markers directly but assesses structural connectivity that may be disrupted by processes such as iron-induced demyelination DTI is the preferred modality for assessing WM integrity and connectivity, which declines with age and is linked to cognitive slowing and reduced executive function. QSM, however, offers insights into how iron deposits affect WM indirectly, as excess iron can lead to oxidative stress, affecting both myelin and connectivity. While PET provides detailed metabolic and biochemical information, it requires radiotracers and involves radiation exposure, which limits its use in regular follow-ups for aging populations. MRI, particularly with QSM and DTI, is non-invasive and radiation-free, allowing for safer, repeated assessments in longitudinal studies. Each modality has strengths that make it valuable in the study of brain aging. PET provides metabolic and molecular insights, QSM enables detailed mapping of iron accumulation, and DTI reveals WM integrity. Together, these tools allow for a comprehensive assessment of structural, functional, and biochemical changes in aging, enhancing our understanding of neurodegenerative processes and potentially informing targeted interventions for age-related cognitive decline. These techniques have provided valuable insights into the

actual process, thereby corroborating the findings of various research studies.

An analysis of QSM studies has shown that the GP consistently exhibits the highest levels of magnetic susceptibility, indicating significant iron accumulation. Conversely, the thalamus tends to show the lowest levels of magnetic susceptibility. This regional difference suggests that various brain areas are affected differently by the aging process. Increased iron content in areas such as the CN, PUT, and SN has been associated with declines in motor function, memory, and executive processing, which are essential for daily activities. For instance, higher iron levels in the CN and PUT have been linked to reduced executive function, while iron buildup in the SN is connected to motor impairments commonly seen in older adults. Furthermore, QSM is useful in assessing WM integrity because of its sensitivity to iron bound to myelin, an essential part of WM. As people age, myelin breaks down, leading to reduced efficiency in neuronal signal transmission, which impacts cognitive speed and executive function. QSM studies have found that WM regions in older individuals often show decreased magnetic susceptibility, indicating myelin degradation. The increase in iron levels with age may accelerate myelin breakdown, resulting in deteriorating WM connectivity and, consequently, impaired cognitive function. Gender differences are notable, with women showing unique patterns post-menopause. Furthermore, increased brain iron concentration correlates with reduced neurite density in task-relevant WM networks, implicating its role in cognitive aging. These insights underline the complex interplay between iron accumulation and brain aging, emphasizing the need for further research to unravel the mechanisms and potential interventions to mitigate age-related cognitive decline.

An additional conclusion proposes that an individual's lifestyle significantly influences the manifestation of aging. For instance, diet and physical activity are recognized as two key risk factors. Evidence suggests that a diet supplemented with vitamins, Polyunsaturated Fatty Acids, flavonoids, and iron chelators could impede the aging process; these nutrients have antioxidant, anti-inflammatory, and iron-lowering properties that may help prevent or reduce ferroptosis by controlling excessive iron buildup in brain tissues. Moreover, active individuals are less susceptible to the repercussions and signs of aging.

Gender is also identified as a factor influencing the aging process, indicating a differential aging pattern in males and females. Several studies suggest that males' total cerebral iron content exceeds that of females. Males also exhibit more significant fluctuations in iron levels with age, particularly in the RN, PUT, and Pulvinar [100].

Given the evident expansion of the elderly population, which poses worldwide concern, it is recommended that future research endeavors explore these factors together. Additionally, the utilization of advanced neuroimaging techniques on larger sample sizes is advocated to enhance the accuracy and reliability of the findings.

Limitations and Future Research

This review's focus on QSM and PET limits its scope, potentially overlooking insights from other modalities like fMRI or DTI, which could reveal additional aspects of brain aging, such as connectivity or metabolic changes. Variability in imaging protocols and limited accessibility of these techniques may also affect generalizability. Future research should explore the mechanisms of iron accumulation in aging and neurodegenerative diseases, develop targeted interventions to reduce iron-related damage, and investigate lifestyle factors, such as diet and exercise, for practical brain health recommendations. Additionally, incorporating biological differences like sex for personalized approaches and advancing QSM and neuroimaging technologies will enhance diagnostic accuracy and deepen understanding of brain aging.

Conclusion

In conclusion, the importance of investigating the aging process and related factors is highlighted in order to gain insight into its underlying mechanisms and develop interventions to slow it down. Research increasingly supports the link between iron accumulation and neuronal degradation, identifying non-heme iron as a significant contributor to neurodegeneration in brain aging. Specifically, increased brain iron levels are associated with increased oxidative stress, mitochondrial dysfunction, and damage to gray matter and WM integrity, all of which impact cognitive and motor functions as individuals age.

QSM has played a crucial role in these discoveries, enabling researchers to map iron deposits and correlate them with brain pathology. The continued advancement of QSM, combined with factors like diet, physical activity, and biological differences such as sex, is expected to enhance our understanding of iron's role in aging. This approach could lead to the development of more targeted strategies to mitigate the adverse effects of iron accumulation and other age-related changes in brain health.

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Table of Abbreviations			
(AD)	Alzheimer's Disease	(apoE)	Apolipoprotein E
(APOE4)	Apolipoprotein E ε4 allele	(CN)	Caudate Nucleus
(CNS)	Central Nervous System	(DN)	Dentate Nuclei
(DGM)	Deep Gray Matter	(FDG)	[18F]-Fluorodeoxyglucose
(fMRI)	Functional MRI	(FTP)	Flortaucipir
(GP)	Globus Pallidus	(GRE)	Gradient Recalled Echo
(MEG)	Magnetoencephalography	(PUT)	Putamen
(MPRAGE)	Magnetization-prepared Rapid Gradient Echo	(MRI)	Magnetic Resonance Imaging
(MS)	Multiple Sclerosis	(PET)	Positron Emission Tomography
(PA)	Physical Activity	(PiB)	Pittsburg Compound
(PD)	Parkinson's Disease	(ppm)	Parts Per Million
(PUFA)	Polyunsaturated Fatty Acids	(QSM)	Quantitative Susceptibility Mapping
(RN)	Red Nucleus	(ROS)	Reactive Oxygen Species
(SN)	Substantia Nigra	(TSPO)	Translocator Protein
(WM)	White Matter	(DTI)	Diffusion Tensor Imaging

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