Yang *et al. Ageing Neur Dis* 2022;2:3
DOI: 10.20517/and.2022.03

Ageing and Neurodegenerative Diseases

Review

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Recent developments in understanding brain aging: sex differences, mechanisms, and implications in diseases

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How to cite this article: Yang J, Qu J, Ma H. Recent developments in understanding brain aging: sex differences, mechanisms, and implications in diseases. *Ageing Neur Dis* 2022;2:3. https://dx.doi.org/10.20517/and.2022.03

Received: 14 Jan 2022 **First Decision:** 18 Feb 2022 **Revised:** 3 Mar 2022 **Accepted:** 16 Mar 2022 **Published:** 29 Mar 2022

Academic Editors: Weidong Le, Pingyi Xu **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

Abstract

Exemplified by the disproportionate cases of Alzheimer's disease among women, many diseases show considerable sexual disparity in the aging process. Given that such a sex bias varies significantly in different neurological conditions, considering sex differences is necessary for the diagnosis as well as the treatment of neurological disorders. However, currently, relatively few studies have specifically focused on sex differences in brain aging or the general aging process, which has prevented the development of precision medicine for these sex-different diseases. Here, we summarize age-related disparities relating to cognitive function and dysfunction for males and females from human cross-sectional and longitudinal studies. By discussing potential anatomical and physiological bases underlying such differences, we highlight the importance of sex for aging studies in this review, which may hopefully shed light on understanding the precise causes of different brain diseases.

Keywords: Sex difference, brain aging, dementia, cognitive decline

INTRODUCTION

According to figures from the World Health Organization (WHO), the number and proportion of people aged 60 and older are expanding and estimated to increase to 1.4 billion by 2030 and 2.1 billion by 2050, up from 1 billion in 2020[1]. The process of aging is associated with both normal and pathologic cognitive changes, which significantly affect older adults' daily life and society. The most recent data suggest that the prevalence of dementia will double in Europe and triple worldwide by 2050. Economic costs for dementia reached 957.56 billion dollars and are set to increase to 2.54 trillion dollars worldwide[2]. Alzheimer's disease (AD) is a main cause of dementia, the related total costs of which will reach 507.49 billion dollars by 2030 in China and 1.89 trillion by 2050[2]. Despite this, the clinical diagnosis of AD still faces many problems. There is a clear lack of precise gold standards for both diagnosis and treatment, and scientists have yet to develop multiple effective therapies for AD, especially for patients suffering in the later stages of the disease. Hence, it is clear that, for AD and other broader age-related conditions, research on aging and age-related diseases requires urgent attention.

During the human aging process, females show longer lifespans overall[3,4] but often also display more frailty than males[5]. For example, women aged 45-79 had a higher frailty index based on standards[6] including 28 variables on function, cognition, co-morbidity, health attitudes and practices, and physical performance measures[7]. This is known as the "male-female health-survival paradox"[8], and the sex variable can make a difference for health risks in males and females. To date, sex factors have attracted wide attention in the studies of human aging. In the discoveries of brain aging, sex bias has been well-recognized in the prevalence of certain brain aging-related diseases. For example, females with AD or other dementias exhibit a two-fold incidence compared with males[9]. Conversely, the prevalence of another progressive and age-related neurodegenerative disorder, Parkinson's disease (PD), is 1.5 times more common in men than women[10]. In addition, sex and gender can affect the risk factors and disease progression of aging-related diseases such as AD[11]. Thus, it is important to understand the sex difference in changes of normal brain aging, which should provide specific clues for understanding the sex-related mechanisms for age-related diseases and, in turn, may facilitate improved and personalized care during aging.

Here, we focus on reviewing the current literature reporting the sex difference in the functional changes (cognitive decline and vulnerability to neurodegenerative diseases), structural changes, and cellular hallmark changes of normal brain aging. To address this, we used the terms "sex difference", "brain aging", "cognitive aging", "brain structure", and keywords for cellular hallmarks of brain aging (mitochondria, oxidative stress, glia, ubiquitin-proteasome system, autophagy, DNA repair, stem cell exhaustion, and aberrant neuronal network activity) to search the literature in databases such as PubMed.

We first briefly review human data relating to the sex difference in cognitive decline and vulnerability to neurodegenerative diseases in the process of normal brain aging. Next, we discuss sex difference in potential anatomical changes underlying functional changes of brain aging with human evidence. Finally, we summarize the discoveries on sex difference in cellular hallmarks such as oxidative stress of brain aging from animal experiments and human data, which may offer clues for better therapeutics to cognitive decline in aging and neurodegenerative diseases.

SEXUAL DIFFERENCES IN VULNERABILITY OF MALES AND FEMALES TO COGNITIVE DECLINE IN AGING AND IN RELATED DISEASES

Sex difference of cognitive decline in normal brain aging

Cognitive function includes a variety of mental processes such as perception, attention, memory, decision making, and language comprehension. General sex differences in specific cognitive functions have been reported, with the most accepted findings being that men outperform women on spatial-based aspects, especially visual-spatial working memory tasks[12], while females excel in verbal memory and location memory tasks[13,14]. These differences seem to remain consistent from adolescents and young adults into older ages[15,16]. In line with previous reports, several studies have demonstrated that certain cognitive functions decline along with the normal process of the aging of the human brain[17,18]. Such studies monitor the trajectories of cognition change along with the process of aging in order to pick up any related changes of cognitive function that occur concurrently with stages of the aging process.

Longitudinal studies have been demonstrated as particularly useful and applicable in the study of both the difference of cognitive performance levels and the rates of cognitive change over time. In line with the results of the cross-sectional studies mentioned above, De Frias *et al.*[19] found that women performed better on episodic memory tasks and men had higher visuospatial ability, and this sex difference was stable across age groups (35-80 years) over a 10-year period. When detecting the cognition decline rate between females and males with aging, although a review published in 2013 which screened 13 longitudinal studies concluded that no sex differences were found in the rate of overall cognitive decline between the ages of 60-80 years[20], there are many other investigations that have shown sex differences existed in some specific cognitive tasks or in much older age (> 80) [Table 1]. Finkel *et al.*[21], for example, found men had a faster linear decline than women on a card rotation test from middle age (50). Another study conducted by Casaletto *et al.*[22] detected the age-related cognitive decline of 314 normal adults (average 69.3) and found that men tended to develop a declining episodic memory trajectory. Meanwhile, in recent longitudinal studies, McCarrey *et al.*[23] administered a series of memory and other cognitive tests to participants from the Baltimore Longitudinal Study of Aging to detect the cognitive change of females and males with age. They found men showed steeper rates of decline on measures of mental status, perceptuomotor speed and integration, and visuospatial ability, but no significantly differing declines on other cognitive abilities tested compared to women[23]. However, when analyzing increased numbers of people of the older age brackets, and after adjusting for age, education, and vascular factors, one study demonstrated that women showed a steeper decline of cognition than men after 80 years old[24]. Finkel *et al.*[21]'s study also demonstrated that women had a faster decline in information tests than men at ages beyond 65, with a much steeper decline after 80. However, McDowell *et al.*[25] showed a trend for a steeper decline in men when compared with women after 80 years. Because of the complexity of human studies, it is still difficult to have a consistent conclusion, and further studies are still warranted. Nevertheless, these findings seem to indicate that women tend to show more cognitive decline at later old age than men (> 80), particularly for some for specific cognition functions, while men may have a faster cognitive decline in earlier old age (50-65).

Limitations and difficulties of human research techniques may contribute to these disparities. Firstly, the backgrounds of individuals may represent differences in aspects such as education[24,26], lifestyle[27], physical activities[28], and weight[29], and these factors not only affect the baseline of individual cognitive function but also affect the rate of cognitive decline. This makes the study on the effect of the single factor of sex on the rate of cognitive decline difficult to isolate. Moreover, in longitudinal studies, subjects are incorporated into such studies from many different age groups, in which case a limited number of subjects will be of the same age, despite a large sample of total subjects being involved. Different cohorts also show different aspects of cognitive aging[30,31]. All these factors may cause discrepancies in results. To distinguish the true effect of sex

Table 1. Longitudinal studies for sex difference in normal cognitive decline

Ref.	Age (year)	Type of cognitive task	Decline rate
Finkel *et al.*[21]	> 65	Information test	F > M
	50-65	Card rotation test	M > F
Casaletto *et al.*[22]	47-99	The California verbal learning test	M > F
McCarrey *et al.*[23]	64.9-69.7	MMSE, fluent language production, digital symbol, card rotation	M > F
Proust-lima *et al.*[24]	> 80	Digit symbol substitution task	F > M
McDowell *et al.*[25]	> 65	Modified mini-mental state (3MS) cognitive Screening test	F > M (institution)
	> 80	Modified mini-mental state (3MS) cognitive Screening test	M > F

F: Female; M: male.

on cognitive decline with aging, larger sample sizes of confirmed similar backgrounds and the same ages should be involved, and the observation durations should be extended for these groups.

Sex differences in vulnerability to aging associated cognitive disorders

Brain aging is a natural process that results in a certain level of associated cognitive decline. However, as the brain ages, it is more susceptible to neurodegenerative diseases such as Alzheimer's disease (AD), Lewy body dementia (LBD), frontotemporal dementia (FTD), or Parkinson's disease (PD). These diseases usually occur in later life, worsening with subsequent aging. They often manifest with increasing age-related cognitive impairment, finally leading to dementia. Unlike the inconsistent results for the sex difference of cognition decline in normal brain aging, relatively consistent results have been demonstrated relating to females and males for some aspects of the vulnerabilities to these diseases [Table 2].

AD is the leading cause of dementia, which accounts for 60%-80% of dementia cases. Over the past 20 years, many studies have investigated sex differences in the risk, incidence, prevalence, or development of AD. For the analysis of risk, the Framingham Heart Study showed that, for a 65-year-old woman, the risk of AD over her remaining lifetime was 21.2%, while for a man, it was 11.6%. Correspondingly, the ratio of female to male risk for AD was noted as about 2:1[32]. For overall numbers, many epidemiological studies of varied global locations also highlighted a higher number of women than men with AD[33,34]. The prevailing explanation for such a difference is that women live longer than men on average, and that the incidences of AD correspond with increased age[32]. The argument could therefore be formulated that any apparent sex-based difference for this disease is simply due to the increased average longevity for women. However, upon a more specific analysis of prevalence, results seem to conflict with the lifespan explanation. Plassman *et al.*[35]'s Aging, Demographics, and Memory Study (ADAMS), including subjects aged 71 years and older from all regions of the USA, showed a higher prevalence of AD in women than in men of corresponding ages. In the 2015 World Alzheimer Report, Prince *et al.*[36] showed that, in East Asia, South Asia, the Caribbean, Western Europe, and Latin America, the prevalence of dementia for men was lower than for women, although no significant difference was noted for other regions. In addition, their review in 2016, summarizing several similar studies from Europe, indicates the same higher prevalence of AD in women[37]. As for the incidence of AD, the conclusion that there is no sex difference has been noted in some studies from the United States[38,39], while others have shown that women tended to have a higher incidence of AD[40]. These disparities may stem from regional and socioeconomic factors and/or cultural effects (such as diet and lifestyle). The 10/66 Dementia Research Group study of dementia in low- and middle-income countries found a higher incidence in women[41], and most studies on European[42,43] and Asian populations[44,45] have also observed a higher incidence in women at an older age. With regards to any sex differences related to the rate of cognitive decline beyond the diagnosis of AD, many studies show that the

Table 2. Sex difference of neurodegenerative diseases

Neurodegenerative diseases	Factors	Sex difference	Ref.
Alzheimer's disease (AD) The leading cause of dementia, which accounts for 60%-80% of dementia cases	Number	F > M	Chêne *et al.*[32] Hebert *et al.*[33] Alzheimer's Association 2021[34]
	Prevalence	F > M	Plassman *et al.*[35] Prince *et al.*[36] Prince *et al.*[37]
		No difference	Prince *et al.*[36] Rocca[152]
	Incidence	F > M	Fitzpatrick *et al.*[40] Prince *et al.*[41] Ruitenberg *et al.*[42] Rizzi *et al.*[43] Chen *et al.*[44] Yamada *et al.*[45]
		F = M (equal)	Tom *et al.*[38] Zahodne *et al.*[39]
	Cognitive decline rate	F > M	Hebert *et al.*[33] Holland *et al.*[46] Tifratene *et al.*[47] Lin *et al.*[48] Laws *et al.*[49] Gamberger *et al.*[50]
Lewy body dementia (LBD) The second most prevalent cause of neurodegenerative dementia	Number	M > F	Nelson *et al.*[54]
	Incidence	M > F	Savica *et al.*[55] Goodman *et al.*[56]
Frontotemporal dementia (FTD) The third most prevalent form of neurodegenerative dementias	Prevalence	M > F	Goodman *et al.*[56] Mercy *et al.*[58]
		F > M	Bernardi *et al.*[59] Ikeda *et al.*[60]
		No difference	Borroni *et al.*[61]
Parkinson's disease (PD) A movement disorder that can also lead to dementia	Prevalence	M > F	Pringsheim *et al.*[63] (worldwide) Hirsch *et al.*[64] Abbas *et al.*[65] GBD 2016 Neurology Collaborators[66]
		No difference	Pringsheim *et al.*[63] (Asia) Taylor *et al.*[67]
	Cognitive decline	M > F	Reekes *et al.*[71]

F: Female; M: male.

cognitive deterioration rate is faster in women than men in the progression of AD[33,46-50]. However, despite this faster progression of the disease in women, several studies have shown that men have an overall shorter lifespan beyond diagnosis with AD, as summarized by a recent review[51].

LBD is a neurodegenerative disease with abnormal *α-synuclein* accumulation (Lewy body proteins) in neurons, which can cause cognitive decline. LBD is the second most frequent form of neurodegenerative dementia. Reviews show the prevalence of LBD ranges 0.3%-24% in the general population and 3%-7% in the patients with dementia[52,53]. In accessing the registry autopsy series from the University of Kentucky Alzheimer's Disease Center and the National Alzheimer's Coordinating Center, researchers found that the number of male patients dying with Lewy body-associated pathologies was three times that of females[54]. Similarly, a study on the population of Olmsted County, Minnesota, showed that men had a higher incidence of LBD than women across the age spectrum[55]. A study on the prevalence of dementia subtypes in United States Medicare showed the same result[56]. FTD is considered the third most frequent form of

neurodegenerative dementia with more relatively young patients than other types of dementia (< 65)[57]. While many studies have demonstrated sex differences in the prevalence of this disorder, no clear consensus has been reached. Studies in the population of Cambridgeshire, UK, and a United States Medicare study both showed greater FTD prevalence in men than women[56,58]. However, many other studies failed to support these results[59-61]. The discrepancy here may be due to difficulties in the exact diagnosis of FTD, which presents with similar clinical symptoms to late onset psychiatric disorders and amyotrophic lateral sclerosis (ALS). Recently, Curtis's meta-analysis focusing on the sex difference of the prevalence of genetic mutations in FTD and ALS indicated a higher prevalence of progranulin (GRN)-muted FTD in female patients but no sex differences in chromosome 9 open reading frame 72 (C9orf72)- and microtubule-associated protein tau related FTD (MFTD), which should further help clarify the sex differences of prevalence of FTD[62]. Another neurogenerative disease is PD. PD is a movement disorder with bradykinesia, rigidity, tremor at rest, gait disturbance, and difficulty with speech. PD can also lead to dementia, and the proportion of patients with PD who are also diagnosed with Parkinson's disease dementia ranges from 10% to 15%. Studies are fairly consistent in demonstrating that there is a higher prevalence of PD presented among men than women from worldwide epidemiological data[63-66], especially in Western and South American populations[10,67-69]. However, there are reports showing the prevalence rates were almost equal between men and women in Asian populations[63,67]. Thus, there appears to be a difference between Asian and Western populations, which may stem from sex different behaviors such as smoking, methodologies, genetics, and ethnicity[65,70]. For the cognitive decline in PD, Reekes *et al.*[71] indicated that males with PD have significantly greater executive and processing speed impairments compared to women.

As mentioned above, the aging brain undergoes cognitive functional change and becomes increasingly susceptible to a number of cognitive diseases. Although no results have consistently or conclusively shown differences in cognitive decline rate between females and males, apparent sex differences have been shown to be involved in the cognitive performance and disease susceptibility of the elderly. In addition, females have been demonstrated as more susceptible to AD, and males are more vulnerable to LBD and PD. The underlying mechanism for such sex-based differences in brain aging behaviors and related diseases is a key area for further study.

BRAIN STRUCTURE AS A BASIS FOR SEX DIFFERENCES IN BRAIN AGING

To explain how function changes with aging, the most widely investigated aspect is the structural changes of the aging brain. With the advantages of noninvasive imaging techniques, researchers were able to study the aging brain in healthy living individuals. As many healthy volunteers were incorporated into such studies, this provided the opportunity to analyze the sex differences of the human brain anatomy relating to aging. Using magnetic resonance imaging, many researchers found more profound age-related decline in cortical grey matter volume in males than females[72-74]. However, there are many investigations that do not support the hypothesis that the effect of aging is accelerated in men and have failed to find age-by-sex interactions in adult and elderly populations[75-77]. When considering the sex differences of subcortical gray matter structure in the aging brain, conclusions are no more consistent [Table 3]. The subcortical structures studied include the basal ganglia (caudate, nucleus accumbens, putamen, and pallidum), thalamus, hippocampus, and amygdala. Among these, the hippocampus is the most studied, and some hippocampus studies have reported that females have larger volumes in the aging brain[78-80] while others have opposing results[81]. In old age, for thalamus, some studies found the male had a larger volume[72,80], while others opposed this[82]. When correcting for brain volume, Li *et al.*[78] found no significant sex difference in the relative volume of thalamus. Similarly, for the caudate, some found females had larger volume[83,84], while others found males had larger volume[78,80]. More consistently, the amygdala[78,85], pallidum[78,80], and putamen[78,80] have been invariably found to be larger in males.

Table 3. Sex difference of subcortical regions in the aging brain of cross-sectional studies

Subcortical regions	Ref.	Age (year)	Sex difference of volume in older age (> 45)	Sex difference of decline rate in older age (> 45)
Hippocampus	Li *et al.*[78]	19-70	F > M (relative volume)	M > F (relative volume)
	Nemeth *et al.*[79]	21-58	F > M	M > F
	Wang *et al.*[80]	19-86	F > M (> 70)	M > F
	Goto *et al.*[81]	41-77	M > F (absolute volume)	F > M (absolute volume)
Thalamus	Sullivan *et al.*[72]	20-85	M > F	Similar
	Li *et al.*[78]	19-70	Similar (relative volume)	Similar (relative volume)
	Wang *et al.*[80]	19-86	M > F	M > F
	Takahashi *et al.*[82]	20 to ≥ 80	F > M	M > F
Caudate nuclei	Li *et al.*[78]	19-70	M > F (relative volume)	F > M (relative volume)
	Wang *et al.*[80]	19-86	M > F	Similar
	Good *et al.*[83]	18-79	F > M	No test
	Luders *et al.*[84]	18-82	F > M	No test
Putamen	Li *et al.*[78]	19-70	M > F (relative volume)	F > M (relative volume)
	Wang *et al.*[80]	19-86	M > F	M > F (right)
Pallium	Li *et al.*[78]	19-70	M > F (relative volume)	F > M (relative volume)
	Wang *et al.*[80]	19-86	M > F	M > F (right)
Accumbens	Wang *et al.*[80]	19-86	Similar	Similar
Amygdala	Li *et al.*[78]	19-70	M > F (relative volume)	F > M (relative volume)
	Cheng *et al.*[85]	20-50	M > F	No test

F: Female; M: male.

Differences in these findings may be due to differences in the age range of subjects evaluated and methods used for analysis. The previous findings of brain structure changes in the aged brain of females and males are mainly based on cross-sectional studies, which only show the status at one specific time or with different status at different specific times. Longitudinal studies may be better suited to address the conflicts in cross-sectional studies. Over the last 15 years, increasing numbers of longitudinal studies have been performed to investigate the rate of brain change with aging. Among them, some studies have paid attention to the sex difference in aging[86-90]. Taki *et al.*[86]'s studies showed the annual percentage change in the grey matter ratio (APC_{GMR}) in the older female group was substantially lower than in the older male group, using such a longitudinal design running over a period of over six years in 381 healthy community-dwelling individuals. Jiang *et al.*[88] chose individuals aged 70-90 years as subjects. After a two-year follow-up, they found that women had thicker cortical regions but greater rates of cortical atrophy[88]. For the structural changes of cortex subregions, Pfefferbaum *et al.*[87] focused on the change of regional brain volume with aging in longitudinal studies. They found a more rapid increase of lateral ventricle volume and Sylvian fissures and more rapid decline of the centrum semiovale, anterior cingulate, parietal and precentral cortices, and thalamus in older men than older women, especially in those beyond 60 years of age[87]. Narvacan *et al.*[89] scanned a cohort of 55 subjects approximately three years apart. While finding that overall males had larger volumes than females for all subcortical structures, no sex differences in trajectories of change were detected[89]. Such differences may stem from longitudinal studies which can be limited by the age range of participants, sex distribution of the samples, or scanning intervals. In a recent study, Vinke *et al.*[90] used the Rotterdam study[91] to understand the different aspects in brain aging of middle- and old-aged males and females based on a large prospective population-based cohort study. Their analysis showed that an earlier acceleration of decrease for normal-appearing white matter volume, gray matter volume, total brain volume, hippocampus volume, and pallidum volume and increased cerebrospinal fluid volume had occurred in men compared with women. Meanwhile, men tended to have a higher prevalence of focal

lesions (microbleeds, lacunes, and cortical infarcts) compared with women. Although shorter time intervals and less time for scanning posed some limitations for the reliable representation of the longitudinal effect of those of older ages, this study, with the largest sample used for aging-related research, provides good background information for understanding the different changes in the female and male brain due to aging.

As for other studies dealing with functional age-related change in the human brain, limitations exist in both cross-sectional and longitudinal studies for investigating how the brain's structure changes with aging. Although no consistent results have been reached for such sex differences in brain structural changes, most studies have indicated that males have accelerated atrophy in the grey matter of the cortex. This may support some findings for the faster cognitive decline in males mentioned above. The noted differences in changes for different subcortical regions may help us to understand why females outperformed males in some specific tasks while males outperformed females in others. In their review, Nemeth *et al.*[79] demonstrated the possible functional consequences of sex difference of the subcortical grey matter, noting that their findings were relevant for dementia occurrence. However, the direct link among brain structures, cognition, and behavior is not currently clear and requires further investigation.

CELLULAR BASIS FOR SEX DIFFERENCES IN BRAIN AGING

Mattson and Arumugam[92] 2018 paper summarizes these findings well and organizes the main aspects of brain aging into nine hallmarks: (1) mitochondrial dysfunction; (2) oxidative damage; (3) impaired cellular "waste disposal" mechanisms (autophagy-lysosome and proteasome functionality); (4) impaired adaptive stress response signaling; (5) impaired DNA repair; (6) aberrant neuronal network activity; (7) dysregulated neuronal Ca^{2+} handling; (8) stem cell exhaustion; and (9) glia cell activation and inflammation. To date, several studies (mainly from animal experiments) have shown sex differences for these hallmarks, indicating possible cellular and molecular mechanisms for sex disparity of brain aging [Figure 1].

Sex difference in mitochondrial dysfunction and oxidative stress with brain aging

The mitochondrion is an important organelle in the cell, which plays crucial roles in ATP production, storage calcium ions, and the regulation of cellular proliferation[93]. Sex difference has been found in many aspects of brain mitochondrial function including morphology, pathways of biogenesis, autophagy, cell death, calcium, and redox homeostasis[94]. However, such results have been mainly based on investigations of the adult brain or injured brain. Investigations on sex differences of brain-based mitochondrial dysfunction related to the normal aging process are relatively sparse. However, sex factors of redox homeostasis have been directly studied relating to brain aging, where the mechanism of the balance of free radical production and antioxidants is required to maintain redox homeostasis.

Upon aging, brain neurons tend to suffer from oxidative damage by excessive generation of free radicals and reduced antioxidant defense. Animal studies showed that, in young adult rats, females exhibit lower release of cytochrome c and lower levels of mitochondrial hydrogen peroxide than males[95]. Moreover, in rats of similar ages, female brain mitochondria generated half the amount of peroxides and imposed dramatically less oxidative damage to mitochondrial DNA than those of males[96]. In contrast, Guevara *et al.*[97,98]'s studies on rat brains of different ages (6, 12, 18, and 24 months old) showed no significant sex-based differences for H_2O_2 production in any age class, despite H_2O_2 production being increased with age in both sexes.

For the antioxidant system, studies on rodents showed that young female brains have higher expression or activities of the antioxidant enzymes SOD and CAT[99-101]. However, upon brain aging, the factors of sex difference relating to oxidative stress become complicated. Although higher antioxidant defense occurred in young female rats, after ovariectomy, mitochondrial peroxide and glutathione (GSH) levels in females

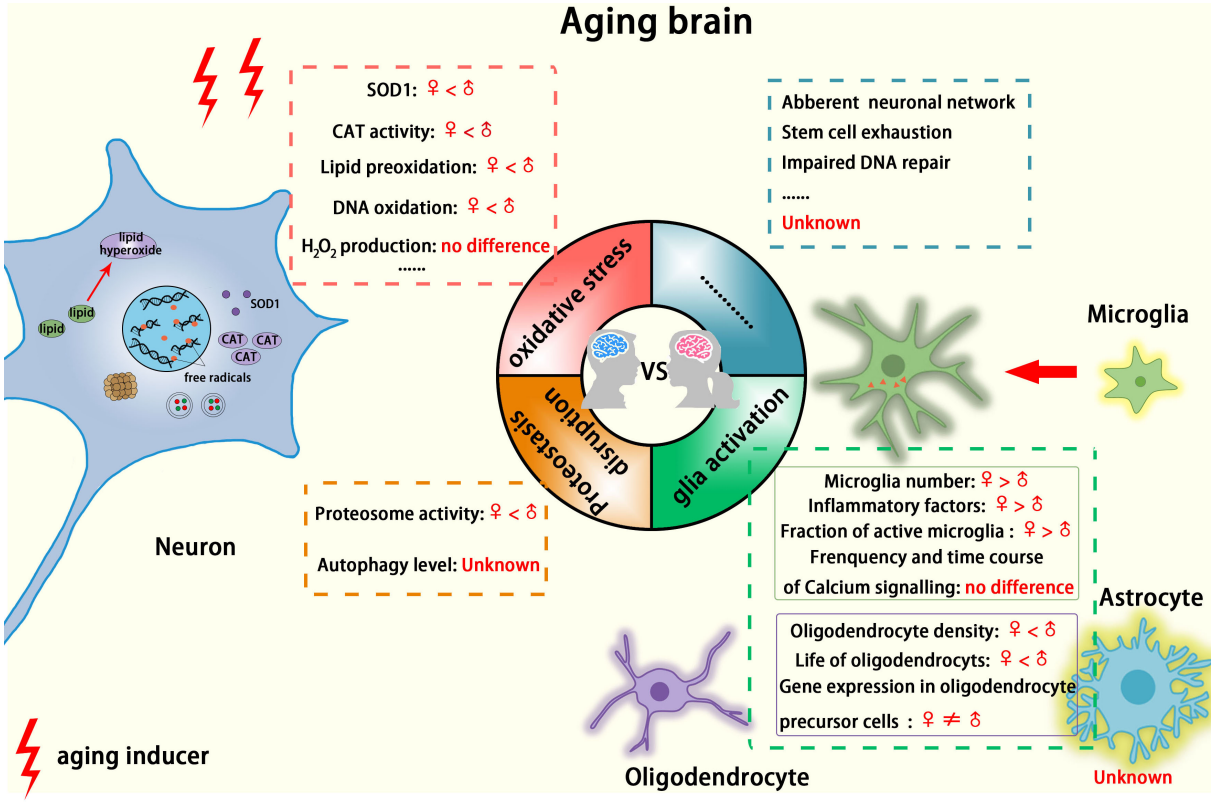

Figure 1. Sex differences implicated in cellular hallmarks of the aging brain. Shown in colored sections and dashed boxes, sex differences may exist in some hallmarks of brain aging.

became similar to those of males[96], indicating decreased antioxidant ability in menopausal female rats. Accordingly, other non-human studies also showed higher CAT activity in the aging (18-20 months) male mouse brain and higher SOD1 protein levels in the brain of aged (28-month-old) males[102]. Similar results were found in Human studies. Viña and Borrás[103] proposed that young females have a better ability to fight against oxidative stress with higher antioxidant levels prior to menopause. Mandal *et al.*[104] also found that young females (± 26 years old) have higher GSH levels than young men in the frontal and parietal cortex. Interestingly, the GSH levels decrease in the brains of older women (56 years old) compared with the younger women[104], indicating that the antioxidant ability changes with aging in women. In line with this, Rekkas *et al.*[105] found that oxidative stress in the brain increased rapidly in perimenopausal women. Bilateral oophorectomy-induced menopause was associated with increases in the GSH/GSSG ratio (increase in GSH, decrease in GSSG) and reduction in SOD and glutathione peroxidase (Gpx) mRNA expression[106], suggesting that women had decreased antioxidant ability after menopause.

When detecting oxidative damage in the brain, several studies in rodents have demonstrated males may exhibit greater oxidative damage, expressed as higher DNA oxidation[107] or higher levels of lipid peroxidation[107-109], than age-matched females over relatively young ages. This may be caused by lower free radical production and higher antioxidant defense in young females. However, other studies show no such sex differences[110,111] or higher oxidative damage in females[100,112]. These differences may stem from the different brain regions under examination or the different times of detection. Guevara *et al.*[97,98]'s studies on rats of different ages (6, 12, 18, and 24 months old) showed lesser oxidative damaged proteins and lipids in female brains, even in old age, an observation which they attributed in part to higher Gpx activity.

Uzun *et al.*[113]'s study also found that protein damages were greater in male brains of 24-month-old rats. However, in the brain of 6-month-old ovariectomy mice, females showed increased levels of lipid peroxidation compared to the sham group[114], indicating increased oxidative damage in postmenopausal females.

Overall, these findings on the sex difference in oxidative stress in the aging brain suggest that young females have a better ability to defend against oxidative stress, but these advantages may be lost upon aging, especially beyond menopause. As reviewed in Grimm *et al.*[115]'s paper, the change of redox state with aging is associated with variation in sex steroid levels. This finding may aid in the understanding of sex differences in vulnerability to neurodegenerative disease[115].

Sex differences in glia cell activation upon brain aging

Glial cells are distinguished from neurons in the brain and play important roles in brain function via facilitating crosstalk with neurons, maintaining the normal function of neurons, and defending against harmful stimuli. There are different types of glial cells in the brain, including astrocytes, microglia, and oligodendrocytes, each with distinct functions. Oligodendrocytes insulate axons and provide them with trophic support[116]; microglia are regarded as macrophages participating in local immunity[117]; and astrocytes provide biochemical support of neuronal activities by facilitating the appropriate glial surroundings in conjunction with microglia[117,118]. Various wide-ranging studies have demonstrated sex differences related to glial cells in physiological conditions or in response to pathological insults[119-121]. However, sex differences in aged glial cells remain relatively under-studied, and the discoveries mainly stem from animal experiments.

Sex differences in microglia are the most studied sex-related aspect in the process of brain aging, with previous studies quantifying changes of microglia in the aging brain[122,123]. Mouton *et al.*[123]'s study showed that, in both young and old mice, females had more astrocytes and microglia in DG and CA1 of the hippocampus than did age-matched male mice. In addition, with the development of sequencing technology, recent studies have paid increasing attention to the gene expression relationships for microglia in aging[124,125]. Mangold *et al.*[126] also detected the sex differences for microglial gene expression in the mouse hippocampus and cortex. They found that inflammatory genes were more highly expressed in microglia of older females than in corresponding older males[126]. Importantly, using single-cell RNA-sequencing analysis, Sala Frigerio *et al.*[127] found that aging or progressive amyloid-β accumulation accelerated the two main activated microglia states and that female mice progressed faster in this than males, which also converged with the pathway of sex differences relating to aging and AD. In addition, Kang *et al.*[128] mentioned in their article that tauopathy, amyloidosis, and aging had been shown to share a common APOE-driven transcriptional signature in microglia, which indicates that the increased expression of many of these transcripts of microglia in older mouse brains may be related to increased susceptibility to Alzheimer's disease in females. As regards to the functions of microglia in aging, one recent study on phagocytosis showed that aged female microglia had a greater ability for phagocytosis of neuronal debris, but they had lost their ability to adapt their phagocytic activity to inflammatory conditions[129]. Another study on microglial function, analyzing microglial Ca^{2+} signaling and process motility, suggested "faster aging" for microglia in female mice[130]. Taken together, the more active/faster aging microglia in older females may render them more vulnerable to some age-related neurodegenerative disease such as AD.

Relatively few studies have focused on astrocytes and oligodendrocytes in aging. Research on astrocytes has mainly been conducted in vitro via the detection of differences in the changes between the sexes under specific stimuli or in response to various pathological insults[131]. No specific analysis of the sex differences

relating to the aging process seems to have been conducted relating to astrocytes. For oligodendrocytes, Cerghet *et al.*[132,133] examined the sex difference of oligodendrocytes in the rat and mouse brain and found that the density of oligodendrocytes in the corpus callosum, fornix, and myelin proteins and myelin gene expression were all greater in males, and shorter life of oligodendrocytes was noted in females, a finding which did not simply represent younger mice and rats, but also held true for old mice. These differences for oligodendrocytes and myelin may be associated with the sex difference in the white matter volume in the adult and aging brain, which is discussed in "**BRAIN STRUCTURE AS A BASIS FOR SEX DIFFERENCES IN BRAIN AGING**". Oligodendrocyte precursor cells can generate new mature oligodendrocytes to defend against myelin impairment in the adult brain. Transcriptomic analyses have identified sex differences in oligodendrocyte precursor cells in the expression of genes encoding for proteins involved in the cell cycle, proliferation, maturation, and myelination, among other functions[134,135]. This difference renders older (12-month-old) female rats with greater abilities of remyelination than males after demyelination lesions[136].

Sex differences in proteasome degradation and autophagy upon brain aging

In most organisms, a balance in the protein system, which forms the basis for gene expression and protein synthesis and degradation, is important for the normal function of cells. Aging often shifts this balance with the subsequently altered gene expressions and protein synthesis and disrupted protein degradation, resulting in some notable pathological features[137]. In recent studies, many molecules have been demonstrated to be associated with brain aging including SFRS11[138], CD22[139], REST[140], and BAZ-2 and SET-6[141], the expressions of which change along with the aging process. However, no particular sex differences have been noted for these. Whether this is due to there not being any notable sex differences, or that this is an aspect yet to be properly examined, remains to be clarified.

Another important part of the protein system is protein degradation, which has been verified to be disrupted with brain aging[142]. In cells, two main protein degradation systems exist, namely the ubiquitin-proteasome system (UPS) and autophagy[143,144]. A few non-human data demonstrate that sex differences exist in these protein degradation systems of the aged brain. Ding and Keller[145]'s study showed that proteasome inhibition occurs with aging in the central nervous system, while Zeng *et al.*[146]'s study demonstrated that, in older (15-month-old) female mice and rats, catalytic activities of the proteasome are decreased in the cortex, striatum, cerebellum, globus pallidus, and substantia nigra with aging. In Jenkin *et al.*[147]'s study, investigators compared the activity of the proteasome in nine tissues of young (3-5-month-old) and middle-aged (10-15-month-old) female and male mice. They found young females showed no significant differences in their proteasome activity in the brain as compared to young males. However, from middle age onwards, males showed significant decreases in proteasome activity with subsequent aging, while no such change was noted for females[147]. One study on older fruit flies showed that basal activities of 20S proteasome had decreased in both female and male fruit-fly heads. However, in young female flies, the proteolytic capacity of the 20S proteasome could be increased via the induction of H_2O_2, but with this effect diminishing for older female flies. However, male flies showed no such age-related adaptation of the 20S proteasome[148]. This indicated the potential for an age-related sex difference for proteasome activity in its primed adaption from external stimuli. In another recent study, old (22-month-old) male rats showed impaired fear memory with impaired UPS activity (reduced phosphorylation of the Rpt6 proteasome subunit and accumulated K48 polyubiquitinated proteins) in the basolateral amygdala (BLA), while no behavioral change was noted for old females. In this study, such changes in the activity-driven markers of UPS activity occurred within the medial prefrontal cortex but not in the BLA of old females[149]. Such an observation of the sex differences of UPS activity in different brain regions of the aged brain aid in the understanding of sex differences related to cognitive decline with aging.

As for autophagy, while no direct articles have reported sex differences in the normal aging brain, multiple studies have demonstrated its role in AD[150]. Many investigations on other tissues (not brain tissue) have shown that females appear to have overall lower levels of autophagy, and ovariectomized animals show increased basal levels of autophagy in several cell types[151]. This highlights the changes in the nature and extent of autophagy after menopause in women. Although more research is needed, considering the results of Jenkin *et al.*[147]'s study, younger females show an overall higher proteostasis capacity, where there may be a particularly well-established balance in the two types of protein degradation systems, but these could then become disrupted upon aging, rendering elderly women more vulnerable to a number of associated diseases.

For the many other hallmarks of brain aging, few studies have paid attention to any potential sex differences. Although many of the above-noted differences in the cellular changes between the female and male aging brains are not fully understood, these discoveries will likely attract increasing numbers of researchers to consider the sex factor and to further illuminate the related cellular mechanisms. These will help link the hormonal effects with those that relate to cognition and behavior, in the process of aging.

CONCLUSION

Sex differences in the brain, as they function in developmental and adult stages, have been widely investigated. However, studies on the sex factors related to the aging brain are lagging behind and deserve increasing attention, particularly under the current situation of a rapidly aging global population. Although there are no consistent general conclusions related to sex differences on cognitive decline with aging, the differences of some aspects of cognitive performance in older adults and the increased vulnerability of females and males to various aspects of dementia are becoming fairly well established, especially for AD and PD where sex is regarded as a primary risk factor for these neurodegenerative diseases. Specifically, many studies have demonstrated that women have a higher prevalence of AD than age-matched men and exhibit faster cognitive decline beyond AD diagnosis. Conversely, almost all recent studies have demonstrated that men have a higher prevalence of PD. However, for treatment, the current interventions for dementia often fail to consider the sex factor. One possible reason may be that the underlying mechanisms of sex difference for the functional changes that occur during the process of brain aging are not yet fully clear and that present techniques and other socioeconomic factors render such factors difficult to examine in detail. However, it is clear that age-related cohorts need to be established and traced to provide information about how human aging-related phenotypes and molecular changes upon aging relate to sex, in order to guide future health improvements. Beyond human-based studies, to unpack the possible structural and cellular mechanisms for sex differences of the aging brain, the use of animal models should be increasingly established, with experiments designed that can incorporate the benefits of the model animal's simple genetic background. With a better understanding of the biological mechanism for the sex differences in brain aging, we can better understand the overall functional changes in the brain, elucidate how sex creates differences in disease risk, lay a stronger foundation for dealing with the newly emerging aspects of neurodegenerative disease, explore more directly the biomarkers for brain aging, and further promote personalized medicine that incorporates the factor of sex for improved and more individualized disease treatment.

DECLARATIONS

Authors' contributions

Made contributions to conception of this review article: Yang J, Ma H
Screened and gathered articles and wrote the abstract and introduction: Qu J

Wrote the other sections and made tables: Yang J

Availability of data and materials
Not applicable.

Financial support and sponsorship
This study was supported by the National Key R&D Program of China to Ma H (grant number 2019YFA0508603); Science and Technology Innovation 2030-Major Project to Ma H (2021ZD0203501); the National Natural Science Foundation of China (grant numbers 81930030, 31771109, and 31722023 to Ma H; 81901154 to Yang J); Project for Hangzhou Medical Disciplines of Excellence; Key Project for Hangzhou Medical Disciplines.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

REFERENCES
1. Aging and health. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Last accessed on 25 Mar 2022].
2. Jia J, Wei C, Chen S, et al. The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimers Dement* 2018;14:483-91. DOI PubMed
3. Sampathkumar NK, Bravo JI, Chen Y, et al. Widespread sex dimorphism in aging and age-related diseases. *Hum Genet* 2020;139:333-56. DOI PubMed PMC
4. Bronikowski AM, Altmann J, Brockman DK, et al. Aging in the natural world: comparative data reveal similar mortality patterns across primates. *Science* 2011;331:1325-8. DOI PubMed PMC
5. Fan J, Yu C, Guo Y, et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. *Lancet Public Health* 2020;5:e650-60. DOI PubMed PMC
6. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr* 2008;8:24. DOI PubMed PMC
7. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: a systematic review and meta-analysis. *Exp Gerontol* 2017;89:30-40. DOI PubMed
8. Oksuzyan A, Petersen I, Stovring H, Bingley P, Vaupel JW, Christensen K. The male-female health-survival paradox: a survey and register study of the impact of sex-specific selection and information bias. *Ann Epidemiol* 2009;19:504-11. DOI PubMed PMC
9. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020-2060). *Alzheimers Dement* 2021;17:1966-75. DOI PubMed
10. Moisan F, Kab S, Mohamed F, et al. Parkinson disease male-to-female ratios increase with age: French nationwide study and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87:952-7. DOI PubMed PMC
11. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. *Alzheimers Dement* 2018;14:1171-83. DOI PubMed PMC
12. Voyer D, Voyer SD, Saint-Aubin J. Sex differences in visual-spatial working memory: a meta-analysis. *Psychon Bull Rev* 2017;24:307-34. DOI PubMed
13. Voyer D, Postma A, Brake B, Imperato-McGinley J. Gender differences in object location memory: a meta-analysis. *Psychon Bull Rev* 2007;14:23-38. DOI PubMed
14. Asperholm M, Högman N, Rafi J, Herlitz A. What did you do yesterday? *Psychol Bull* 2019;145:785-821. DOI PubMed
15. Jansen P, Kaltner S. Object-based and egocentric mental rotation performance in older adults: the importance of gender differences and motor ability. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2014;21:296-316. DOI PubMed
16. Munro CA, Winicki JM, Schretlen DJ, et al. Sex differences in cognition in healthy elderly individuals. *Neuropsychol Dev Cogn B*

Aging Neuropsychol Cogn 2012;19:759-68. DOI PubMed PMC
17. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med* 2013;29:737-52. DOI PubMed PMC
18. Salthouse TA. Trajectories of normal cognitive aging. *Psychol Aging* 2019;34:17-24. DOI PubMed PMC
19. de Frias CM, Nilsson LG, Nilsson A. Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2006;13:574-87. DOI
20. Ferreira L, Ferreira Santos-Galduróz R, Ferri CP, Fernandes Galduróz JC. Rate of cognitive decline in relation to sex after 60 years-of-age: a systematic review. *Geriatr Gerontol Int* 2014;14:23-31. DOI PubMed
21. Finkel D, Reynolds CA, Berg S, Pedersen NL. Surprising lack of sex differences in normal cognitive aging in twins. *Int J Aging Hum Dev* 2006;62:335-57. DOI PubMed
22. Casaletto KB, Elahi FM, Staffaroni AM, et al. Cognitive aging is not created equally: differentiating unique cognitive phenotypes in "normal" adults. *Neurobiol Aging* 2019;77:13-9. DOI PubMed PMC
23. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging* 2016;31:166-75. DOI PubMed PMC
24. Proust-Lima C, Amieva H, Letenneur L, Orgogozo JM, Jacqmin-Gadda H, Dartigues JF. Gender and education impact on brain aging: a general cognitive factor approach. *Psychol Aging* 2008;23:608-20. DOI PubMed
25. McDowell I, Xi G, Lindsay J, Tuokko H. Canadian study of health and aging: study description and patterns of early cognitive decline. *Aging, Neuropsychology, and Cognition* 2004;11:149-68. DOI
26. Wilson RS, Hebert LE, Scherr PA, Barnes LL, Mendes de Leon CF, Evans DA. Educational attainment and cognitive decline in old age. *Neurology* 2009;72:460-5. DOI PubMed PMC
27. Yu F, Ryan LH, Schaie KW, Willis SL, Kolanowski A. Factors associated with cognition in adults: the Seattle Longitudinal Study. *Res Nurs Health* 2009;32:540-50. DOI PubMed PMC
28. Finkel D, Andel R, Gatz M, Pedersen NL. The role of occupational complexity in trajectories of cognitive aging before and after retirement. *Psychol Aging* 2009;24:563-73. DOI PubMed PMC
29. Noh HM, Han J, Kim YJ, Jung JH, Roh YK, Song HJ. Sex differences in the relationship between cognitive impairment and overweight or obesity in late life: a 3-year prospective study. *Medicine (Baltimore)* 2019;98:e14736. DOI PubMed PMC
30. Gerstorf D, Ram N, Hoppmann C, Willis SL, Schaie KW. Cohort differences in cognitive aging and terminal decline in the Seattle Longitudinal Study. *Dev Psychol* 2011;47:1026-41. DOI PubMed PMC
31. Karlsson P, Thorvaldsson V, Skoog I, Gudmundsson P, Johansson B. Birth cohort differences in fluid cognition in old age: comparisons of trends in levels and change trajectories over 30 years in three population-based samples. *Psychol Aging* 2015;30:83-94. DOI PubMed
32. Chêne G, Beiser A, Au G, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement* 2015;11:310-20. DOI PubMed PMC
33. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology* 2013;80:1778-83. DOI PubMed PMC
34. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* 2021;17:327-406. DOI PubMed
35. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29:125-32. DOI PubMed PMC
36. Wimo A, Ali GC, Guerchet M, Prince M, Prina M, Wu YT; Alzheimer's Disease International. World Alzheimer Report 2015 - The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. Available from: https://www.alzint.org/resource/world-alzheimer-report-2015/ [Last accessed on 25 Mar 2022].
37. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther* 2016;8:23. DOI PubMed PMC
38. Tom SE, Hubbard RA, Crane PK, et al. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. *Am J Public Health* 2015;105:408-13. DOI PubMed PMC
39. Zahodne LB, Schofield PW, Farrell MT, Stern Y, Manly JJ. Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. *Neuropsychology* 2014;28:238-46. DOI PubMed PMC
40. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc* 2004;52:195-204. DOI PubMed
41. Prince M, Acosta D, Ferri CP, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet* 2012;380:50-8. DOI PubMed PMC
42. Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MM. Incidence of dementia: does gender make a difference? *Neurobiol Aging* 2001;22:575-80. DOI PubMed
43. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int* 2014;2014:908915. DOI PubMed PMC
44. Chen R, Hu Z, Wei L, Ma Y, Liu Z, Copeland JR. Incident dementia in a defined older Chinese population. *PLoS One* 2011;6:e24817. DOI PubMed PMC
45. Yamada M, Mimori Y, Kasagi F, et al. Incidence of dementia, Alzheimer disease, and vascular dementia in a Japanese population: Radiation Effects Research Foundation adult health study. *Neuroepidemiology* 2008;30:152-60. DOI PubMed
46. Holland D, Desikan RS, Dale AM, McEvoy LK; Alzheimer's Disease Neuroimaging Initiative. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR Am J Neuroradiol* 2013;34:2287-93. DOI PubMed PMC
47. Tifratene K, Robert P, Metelkina A, Pradier C, Dartigues JF. Progression of mild cognitive impairment to dementia due to AD in

clinical settings. *Neurology* 2015;85:331-8. DOI PubMed

48. Lin FC, Chuang YS, Hsieh HM, et al. Early statin use and the progression of Alzheimer disease: a total population-based case-control study. *Medicine (Baltimore)* 2015;94:e2143. DOI PubMed PMC
49. Laws KR, Irvine K, Gale TM. Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry* 2016;6:54-65. DOI PubMed PMC
50. Gamberger D, Lavrač N, Srivatsa S, Tanzi RE, Doraiswamy PM. Identification of clusters of rapid and slow decliners among subjects at risk for Alzheimer's disease. *Sci Rep* 2017;7:6763. DOI PubMed PMC
51. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013;28:1109-24. DOI PubMed
52. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med* 2014;44:673-83. DOI PubMed
53. Hogan DB, Fiest KM, Roberts JI, et al. The prevalence and incidence of dementia with Lewy bodies: a systematic review. *Can J Neurol Sci* 2016;43 Suppl 1:S83-95. DOI PubMed
54. Nelson PT, Schmitt FA, Jicha GA, et al. Association between male gender and cortical Lewy body pathology in large autopsy series. *J Neurol* 2010;257:1875-81. DOI PubMed PMC
55. Savica R, Grossardt BR, Bower JH, Boeve BF, Ahlskog JE, Rocca WA. Incidence of dementia with Lewy bodies and Parkinson disease dementia. *JAMA Neurol* 2013;70:1396-402. DOI PubMed PMC
56. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement* 2017;13:28-37. DOI PubMed PMC
57. Bang J, Spina S, Miller BL. Frontotemporal dementia. *Lancet* 2015;386:1672-82. DOI PubMed PMC
58. Mercy L, Hodges JR, Dawson K, Barker RA, Brayne C. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology* 2008;71:1496-9. DOI PubMed
59. Bernardi L, Frangipane F, Smirne N, et al. Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in southern Italy. *Neurobiol Aging* 2012;33:2948.e1-2948.e10. DOI PubMed PMC
60. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* 2004;17:265-8. DOI PubMed
61. Borroni B, Alberici A, Grassi M, et al. Is frontotemporal lobar degeneration a rare disorder? *J Alzheimers Dis* 2010;19:111-6. DOI PubMed
62. Curtis AF, Masellis M, Hsiung GR, et al. Sex differences in the prevalence of genetic mutations in FTD and ALS: a meta-analysis. *Neurology* 2017;89:1633-42. DOI PubMed PMC
63. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014;29:1583-90. DOI PubMed
64. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology* 2016;46:292-300. DOI PubMed
65. Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease-East versus West. *Mov Disord Clin Pract* 2018;5:14-28. DOI PubMed PMC
66. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:459-80. DOI PubMed PMC
67. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:905-6. DOI PubMed PMC
68. de Lau LM, Verbaan D, Marinus J, van Hilten JJ. Survival in Parkinson's disease. Relation with motor and non-motor features. *Parkinsonism Relat Disord* 2014;20:613-6. DOI PubMed
69. Pinter B, Diem-Zangerl A, Wenning GK, et al. Mortality in Parkinson's disease: a 38-year follow-up study. *Mov Disord* 2015;30:266-9. DOI PubMed
70. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 2016;15:1257-72. DOI PubMed
71. Reekes TH, Higginson CI, Ledbetter CR, Sathivadivel N, Zweig RM, Disbrow EA. Sex specific cognitive differences in Parkinson disease. *NPJ Parkinsons Dis* 2020;6:7. DOI PubMed PMC
72. Sullivan EV, Rosenbloom M, Serventi KL, Pfefferbaum A. Effects of age and sex on volumes of the thalamus, pons, and cortex. *Neurobiol Aging* 2004;25:185-92. DOI PubMed
73. DeCarli C, Massaro J, Harvey D, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging* 2005;26:491-510. DOI PubMed
74. Ikram MA, Vrooman HA, Vernooij MW, et al. Brain tissue volumes in the general elderly population. The Rotterdam Scan Study. *Neurobiol Aging* 2008;29:882-90. DOI PubMed
75. Salat DH, Tuch DS, Greve DN, et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol Aging* 2005;26:1215-27. DOI PubMed
76. Lemaître H, Crivello F, Grassiot B, Alpérovitch A, Tzourio C, Mazoyer B. Age- and sex-related effects on the neuroanatomy of healthy elderly. *Neuroimage* 2005;26:900-11. DOI PubMed
77. Jäncke L, Mérillat S, Liem F, Hänggi J. Brain size, sex, and the aging brain. *Hum Brain Mapp* 2015;36:150-69. DOI PubMed PMC
78. Li W, van Tol MJ, Li M, et al. Regional specificity of sex effects on subcortical volumes across the lifespan in healthy aging. *Hum Brain Mapp* 2014;35:238-47. DOI PubMed PMC

79. Nemeth VL, Must A, Horvath S, Király A, Kincses ZT, Vécsei L. Gender-specific degeneration of dementia-related subcortical structures throughout the lifespan. *J Alzheimers Dis* 2017;55:865-80. DOI PubMed
80. Wang Y, Xu Q, Luo J, Hu M, Zuo C. Effects of age and sex on subcortical volumes. *Front Aging Neurosci* 2019;11:259. DOI PubMed PMC
81. Goto M, Abe O, Miyati T, et al. Accelerated hippocampal volume reduction in post-menopausal women: an additional study with Atlas-based method. *Radiol Phys Technol* 2011;4:185-8. DOI PubMed
82. Takahashi R, Ishii K, Kakigi T, Yokoyama K. Gender and age differences in normal adult human brain: voxel-based morphometric study. *Hum Brain Mapp* 2011;32:1050-8. DOI PubMed PMC
83. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* 2001;14:685-700. DOI PubMed
84. Luders E, Gaser C, Narr KL, Toga AW. Why sex matters: brain size independent differences in gray matter distributions between men and women. *J Neurosci* 2009;29:14265-70. DOI PubMed PMC
85. Cheng Y, Chou KH, Decety J, et al. Sex differences in the neuroanatomy of human mirror-neuron system: a voxel-based morphometric investigation. *Neuroscience* 2009;158:713-20. DOI PubMed
86. Taki Y, Kinomura S, Sato K, Goto R, Kawashima R, Fukuda H. A longitudinal study of gray matter volume decline with age and modifying factors. *Neurobiol Aging* 2011;32:907-15. DOI PubMed
87. Pfefferbaum A, Rohlfing T, Rosenbloom MJ, Chu W, Colrain IM, Sullivan EV. Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. *Neuroimage* 2013;65:176-93. DOI PubMed PMC
88. Jiang J, Sachdev P, Lipnicki DM, et al. A longitudinal study of brain atrophy over two years in community-dwelling older individuals. *Neuroimage* 2014;86:203-11. DOI PubMed
89. Narvacan K, Treit S, Camicioli R, Martin W, Beaulieu C. Evolution of deep gray matter volume across the human lifespan. *Hum Brain Mapp* 2017;38:3771-90. DOI PubMed PMC
90. Vinke EJ, de Groot M, Venkatraghavan V, et al. Trajectories of imaging markers in brain aging: the Rotterdam Study. *Neurobiol Aging* 2018;71:32-40. DOI PubMed
91. Ikram MA, Brusselle GGO, Murad SD, et al. The Rotterdam Study: 2018 update on objectives, design and main results. *Eur J Epidemiol* 2017;32:807-50. DOI PubMed PMC
92. Mattson MP, Arumugam TV. Hallmarks of brain aging: adaptive and Pathological modification by metabolic states. *Cell Metab* 2018;27:1176-99. DOI PubMed PMC
93. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. *Nat Rev Mol Cell Biol* 2012;13:566-78. DOI PubMed
94. Demarest TG, McCarthy MM. Sex differences in mitochondrial (dys)function: Implications for neuroprotection. *J Bioenerg Biomembr* 2015;47:173-88. DOI PubMed PMC
95. Lloret A, Badía MC, Mora NJ, et al. Gender and age-dependent differences in the mitochondrial apoptogenic pathway in Alzheimer's disease. *Free Radic Biol Med* 2008;44:2019-25. DOI PubMed
96. Borrás C, Sastre J, García-sala D, Lloret A, Pallardó FV, Viña J. Mitochondria from females exhibit higher antioxidant gene expression and lower oxidative damage than males. *Free Radic Biol Med* 2003;34:546-52. DOI PubMed
97. Guevara R, Santandreu FM, Valle A, Gianotti M, Oliver J, Roca P. Sex-dependent differences in aged rat brain mitochondrial function and oxidative stress. *Free Radic Biol Med* 2009;46:169-75. DOI PubMed
98. Guevara R, Gianotti M, Oliver J, Roca P. Age and sex-related changes in rat brain mitochondrial oxidative status. *Exp Gerontol* 2011;46:923-8. DOI PubMed
99. Gaignard P, Savouroux S, Liere P, et al. Effect of sex differences on brain mitochondrial function and its suppression by ovariectomy and in aged mice. *Endocrinology* 2015;156:2893-904. DOI PubMed
100. Dkhil MA, Al-Shaebi EM, Lubbad MY, Al-Quraishy S. Impact of sex differences in brain response to infection with Plasmodium berghei. *Parasitol Res* 2016;115:415-22. DOI PubMed
101. Khalifa AR, Abdel-Rahman EA, Mahmoud AM, et al. Sex-specific differences in mitochondria biogenesis, morphology, respiratory function, and ROS homeostasis in young mouse heart and brain. *Physiol Rep* 2017;5:e13125. DOI PubMed PMC
102. Ali SS, Xiong C, Lucero J, Behrens MM, Dugan LL, Quick KL. Gender differences in free radical homeostasis during aging: shorter-lived female C57BL6 mice have increased oxidative stress. *Aging Cell* 2006;5:565-74. DOI PubMed
103. Viña J, Borrás C. Women live longer than men: understanding molecular mechanisms offers opportunities to intervene by using estrogenic compounds. *Antioxid Redox Signal* 2010;13:269-78. DOI PubMed
104. Mandal PK, Tripathi M, Sugunan S. Brain oxidative stress: detection and mapping of anti-oxidant marker 'Glutathione' in different brain regions of healthy male/female, MCI and Alzheimer patients using non-invasive magnetic resonance spectroscopy. *Biochem Biophys Res Commun* 2012;417:43-8. DOI PubMed
105. Rekkas PV, Wilson AA, Lee VW, et al. Greater monoamine oxidase a binding in perimenopausal age as measured with carbon 11-labeled harmine positron emission tomography. *JAMA Psychiatry* 2014;71:873-9. DOI PubMed PMC
106. Bellanti F, Matteo M, Rollo T, et al. Sex hormones modulate circulating antioxidant enzymes: impact of estrogen therapy. *Redox Biol* 2013;1:340-6. DOI PubMed PMC
107. Candeias E, Duarte AI, Sebastião I, et al. Middle-aged diabetic females and males present distinct susceptibility to Alzheimer disease-like pathology. *Mol Neurobiol* 2017;54:6471-89. DOI PubMed

108. Sobocanec S, Balog T, Kusić B, Sverko V, Sarić A, Marotti T. Differential response to lipid peroxidation in male and female mice with age: correlation of antioxidant enzymes matters. *Biogerontology* 2008;9:335-43. DOI PubMed
109. Silva TLA, Braz GRF, Silva SCA, et al. Serotonin transporter inhibition during neonatal period induces sex-dependent effects on mitochondrial bioenergetics in the rat brainstem. *Eur J Neurosci* ;2018:1620-34. DOI PubMed
110. Cole TB, Coburn J, Dao K, et al. Sex and genetic differences in the effects of acute diesel exhaust exposure on inflammation and oxidative stress in mouse brain. *Toxicology* 2016;374:1-9. DOI PubMed PMC
111. Monte AS, Mello BSF, Borella VCM, et al. Two-hit model of schizophrenia induced by neonatal immune activation and peripubertal stress in rats: study of sex differences and brain oxidative alterations. *Behav Brain Res* 2017;331:30-7. DOI PubMed
112. Al-Gubory KH, Garrel C. Sex-specific divergence of antioxidant pathways in fetal brain, liver, and skeletal muscles. *Free Radic Res* 2016;50:366-73. DOI PubMed
113. Uzun H, Kayali R, Cakatay U. The chance of gender dependency of oxidation of brain proteins in aged rats. *Arch Gerontol Geriatr* 2010;50:16-9. DOI PubMed
114. Yao J, Irwin R, Chen S, Hamilton R, Cadenas E, Brinton RD. Ovarian hormone loss induces bioenergetic deficits and mitochondrial β-amyloid. *Neurobiol Aging* 2012;33:1507-21. DOI PubMed PMC
115. Grimm A, Mensah-Nyagan AG, Eckert A. Alzheimer, mitochondria and gender. *Neurosci Biobehav Rev* 2016;67:89-101. DOI PubMed
116. Serrano-Regal MP, Bayón-Cordero L, Ordaz RP, et al. Expression and function of GABA receptors in myelinating cells. *Front Cell Neurosci* 2020;14:256. DOI PubMed PMC
117. Bernaus A, Blanco S, Sevilla A. Glia crosstalk in neuroinflammatory diseases. *Front Cell Neurosci* 2020;14:209. DOI PubMed PMC
118. Augusto-Oliveira M, Arrifano GP, Takeda PY, et al. Astroglia-specific contributions to the regulation of synapses, cognition and behaviour. *Neurosci Biobehav Rev* 2020;118:331-57. DOI PubMed
119. Thion MS, Low D, Silvin A, et al. Microbiome influences prenatal and adult microglia in a sex-specific manner. *Cell* 2018;172:500-516.e16. DOI PubMed PMC
120. Villa A, Gelosa P, Castiglioni L, et al. Sex-specific features of microglia from adult mice. *Cell Rep* 2018;23:3501-11. DOI PubMed PMC
121. Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD. Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. *Glia* 2017;65:1504-20. DOI PubMed PMC
122. Hayakawa N, Kato H, Araki T. Age-related changes of astorocytes, oligodendrocytes and microglia in the mouse hippocampal CA1 sector. *Mech Ageing Dev* 2007;128:311-6. DOI PubMed
123. Mouton PR, Long JM, Lei D, et al. Age and gender effects on microglia and astrocyte numbers in brains of mice. *Brain Res* 2002;956:30-5. DOI PubMed
124. Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K. Microglia derived from aging mice exhibit an altered inflammatory profile. *Glia* 2007;55:412-24. DOI PubMed
125. Bonham LW, Sirkis DW, Yokoyama JS. The transcriptional landscape of microglial genes in aging and neurodegenerative disease. *Front Immunol* 2019;10:1170. DOI PubMed PMC
126. Mangold CA, Wronowski B, Du M, et al. Sexually divergent induction of microglial-associated neuroinflammation with hippocampal aging. *J Neuroinflammation* 2017;14:141. DOI PubMed PMC
127. Sala Frigerio C, Wolfs L, Fattorelli N, et al. The major risk factors for Alzheimer's disease: age, sex, and genes modulate the microglia response to Aβ plaques. *Cell Rep* 2019;27:1293-1306.e6. DOI PubMed PMC
128. Kang SS, Ebbert MTW, Baker KE, et al. Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid, and tau. *J Exp Med* 2018;215:2235-45. DOI PubMed PMC
129. Yanguas-Casás N, Crespo-Castrillo A, Arevalo MA, Garcia-Segura LM. Aging and sex: impact on microglia phagocytosis. *Aging Cell* 2020;19:e13182. DOI PubMed PMC
130. Del Moral M, Fröhlich N, Figarella K, Mojtahedi N, Garaschuk O. Effect of caloric restriction on the in vivo functional properties of aging microglia. *Front Immunol* 2020;11:750. DOI PubMed PMC
131. Chowen JA, Garcia-Segura LM. Role of glial cells in the generation of sex differences in neurodegenerative diseases and brain aging. *Mech Ageing Dev* 2021;196:111473. DOI PubMed
132. Cerghet M, Skoff RP, Bessert D, Zhang Z, Mullins C, Ghandour MS. Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents. *J Neurosci* 2006;26:1439-47. DOI PubMed PMC
133. Cerghet M, Skoff RP, Swamydas M, Bessert D. Sexual dimorphism in the white matter of rodents. *J Neurol Sci* 2009;286:76-80. DOI PubMed PMC
134. Young KM, Psachoulia K, Tripathi RB, et al. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. *Neuron* 2013;77:873-85. DOI PubMed PMC
135. Yasuda K, Maki T, Kinoshita H, et al. Sex-specific differences in transcriptomic profiles and cellular characteristics of oligodendrocyte precursor cells. *Stem Cell Res* 2020;46:101866. DOI PubMed
136. Li WW, Penderis J, Zhao C, Schumacher M, Franklin RJ. Females remyelinate more efficiently than males following demyelination in the aged but not young adult CNS. *Exp Neurol* 2006;202:250-4. DOI
137. Anisimova AS, Alexandrov AI, Makarova NE, Gladyshev VN, Dmitriev SE. Protein synthesis and quality control in aging. *Aging (Albany NY)* 2018;10:4269-88. DOI PubMed PMC
138. Raihan O, Brishti A, Li Q, et al. SFRS11 loss leads to aging-associated cognitive decline by modulating LRP8 and ApoE. *Cell Rep*

2019;28:78-90.e6. DOI PubMed

139. Pluvinage JV, Haney MS, Smith BAH, et al. CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. *Nature* 2019;568:187-92. DOI PubMed PMC
140. Zullo JM, Drake D, Aron L, et al. Regulation of lifespan by neural excitation and REST. *Nature* 2019;574:359-64. DOI PubMed PMC
141. Yuan J, Chang SY, Yin SG, et al. Two conserved epigenetic regulators prevent healthy ageing. *Nature* 2020;579:118-22. DOI PubMed
142. Tsuji T, Shimohama S. Protein degradation in Alzheimer's disease and aging of the brain. *Prog Mol Subcell Biol* 2002;29:43-60. DOI PubMed
143. Galluzzi L, Baehrecke EH, Ballabio A, et al. Molecular definitions of autophagy and related processes. *EMBO J* 2017;36:1811-36. DOI PubMed PMC
144. VerPlank JJS, Goldberg AL. Regulating protein breakdown through proteasome phosphorylation. *Biochem J* 2017;474:3355-71. DOI PubMed PMC
145. Ding Q, Keller JN. Proteasomes and proteasome inhibition in the central nervous system. *Free Radic Biol Med* 2001;31:574-84. DOI PubMed
146. Zeng BY, Medhurst AD, Jackson M, Rose S, Jenner P. Proteasomal activity in brain differs between species and brain regions and changes with age. *Mech Ageing Dev* 2005;126:760-6. DOI PubMed
147. Jenkins EC, Shah N, Gomez M, et al. Proteasome mapping reveals sexual dimorphism in tissue-specific sensitivity to protein aggregations. *EMBO Rep* 2020;21:e48978. DOI PubMed PMC
148. Pomatto LCD, Wong S, Carney C, Shen B, Tower J, Davies KJA. The age- and sex-specific decline of the 20s proteasome and the Nrf2/CncC signal transduction pathway in adaption and resistance to oxidative stress in Drosophila melanogaster. *Aging (Albany NY)* 2017;9:1153-85. DOI PubMed PMC
149. Dulka BN, Trask S, Helmstetter FJ. Age-related memory impairment and sex-specific alterations in phosphorylation of the Rpt6 proteasome subunit and polyubiquitination in the basolateral amygdala and medial prefrontal cortex. *Front Aging Neurosci* 2021;13:656944. DOI PubMed PMC
150. Li Q, Liu Y, Sun M. Autophagy and Alzheimer's disease. *Cell Mol Neurobiol* 2017;37:377-88. DOI PubMed
151. Congdon EE. Sex differences in autophagy contribute to female vulnerability in Alzheimer's disease. *Front Neurosci* 2018;12:372. DOI PubMed PMC
152. Rocca WA. Time, sex, gender, history, and dementia. *Alzheimer Dis Assoc Disord* 2017;31:76-9. DOI PubMed PMC