Review

Sex Differences in Alzheimer's Disease: Where Do We Stand?

André de Macêdo Medeiros[a,b] and Regina Helena Silva[a,*]
[a]*Behavioral Neuroscience Laboratory, Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*
[b]*Center of Health and Biological Sciences, Universidade Federal Rural do Semiárido, Mossoró, Brazil*

Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder that drastically compromises patients' and relatives' quality of life, besides being a significant economic burden to global public health. Its pathophysiology is not completely elucidated yet, hence, the current therapies are restricted to treating the symptoms. Over the years, several epidemiological studies have shown disproportionalities in AD when sex is considered, which has encouraged researchers to investigate the potentiality of sex as a risk factor. Studies in rodent models have been used to investigate mechanistic basis of sex differences in AD, as well as the development of possible new sex-specific therapeutic strategies. However, full knowledge on factors related to this sexual dimorphism remains to be unraveled. Some findings point to differences in genetic and developmental backgrounds either earlier in life or in the aging brain. Herein we summarize the multisystemic framework behind the sex differences in AD and discuss the possible mechanisms involved in these differences raised by the literature so far in an integrative perspective.

Keywords: Aging, animal models, hormones, humans, immune system, oxidative stress, stress

INTRODUCTION

Alzheimer's disease (AD) causes emotional, physical, social, and financial consequences for patients and their families, and the complexity of its etiology remains to be clarified. AD is the most common form of dementia, and memory loss is the key symptom present in the patients [1]. Even though recall of facts from the remote past (long-term memory) is preserved, they cannot remember events that happened minutes before (short-term memory). In addition, with the progression of the disease, patients find difficulties in everyday life (e.g., spatial disorientation and language disorders) which can be accompanied by comorbidities such as depression, irritability, and delusions [2]. AD is an irreversible age-related disease, and its risk increases dramatically over the years [3]. According to the US Center for Disease Control and Prevention (2001), AD is the eighth leading cause of death in the United States. Studies have predicted that the AD prevalence will triple in the next 50 years to approximately 14 million Americans [4]. The number of the AD cases on the European continent is also high [5] and the total cost of care for these patients exceeds those of cancer and cardiovascular disease together [6, 7]. Worldwide, AD is the most prevalent disease among neurodegenerative disorders [8]. In 2005, 24.2 million people had dementia (70% of which were assigned to AD) and 4.6 million new cases were counted each year since then. Latin America has the third highest prevalence of AD cases (4.9%), behind North America (6.4%) and Western

*Correspondence to: Regina Helena Silva, Department of Pharmacology, Universidade Federal de São Paulo, Rua Botucatu, 862 – Edifício Leal Prado, São Paulo, SP, CEP 04023062, Brazil. E-mails: reginahsilva@gmail.com (R.H. Silva); andre.medeiros@ufersa.edu.br and andredemacedomedeiros@gmail.com (A. de Macêdo Medeiros).

Europe (5.4%), and has the second highest incidence rate—9.2 in 1000 individuals in the population [9]. In Brazil, the prevalence and incidence of dementia are similar to that reported in other countries [10–12].

AD can arise at middle age, but usually affects people over 65 years. The early-onset familial form of AD is rare (about 4–5% of all cases), and is related to genetic heritability [13]. On the other hand, the most common late-onset form (sporadic AD) is attributed to many triggering genetic, developmental, and environmental factors. Indeed, sporadic AD has several risk factors: age, sex, family history, depression, brain injury (traumas), increased allelic frequency of apolipoprotein E (ApoE), solvent exposure, low educational levels, and genetic mutations [2]. Existing treatments are palliative; thus, studies have been focusing on possible new drugs that would reduce disease progression and delay the appearance of the symptoms. Part of the constraints in the search of significant therapeutic targets for neuroprotective actions is the lack of a complete understanding of AD pathogenesis. The deposition of Aβ peptides [14], Aβ oligomers-induced toxicity [15], tau protein hyperphosphorylation and neurofibrillary tangles (NFT) [16], mitochondrial damage, oxidative stress and metal ions deregulation [17, 18], neuropeptides unbalance [19, 20], exacerbated neuroinflammation [14], cerebral alterations in calcium signaling and glucose metabolism (for review, see [21]) are among the hypotheses that have been proposed in the last decades to explain AD pathophysiology. Figure 1 summarizes the elements involved in the AD pathophysiological mechanisms, which may or may not follow a chronological sequence. It is recognized that they interact with each other, playing specific roles in this multifactorial process that lead to a common outcome. Although all of the aforementioned hypotheses are reasonable explanations to the variety of abnormalities found in AD, more research is needed in order to stablish causal elements and their relationship with the risk factors that have been already linked to the disease.

One of the potential risk factors that has attracted attention of AD researchers is sex. The National Institute of Health Office of Research on Women's Health recently highlighted the need for addressing sex differences in AD research [22]. Indeed, a greater investigation of AD sex differences has been observed in recent years and studies on this topic have grown. From the epidemiological perspective, there are important controversies, with data on prevalence between the sexes being more consensual
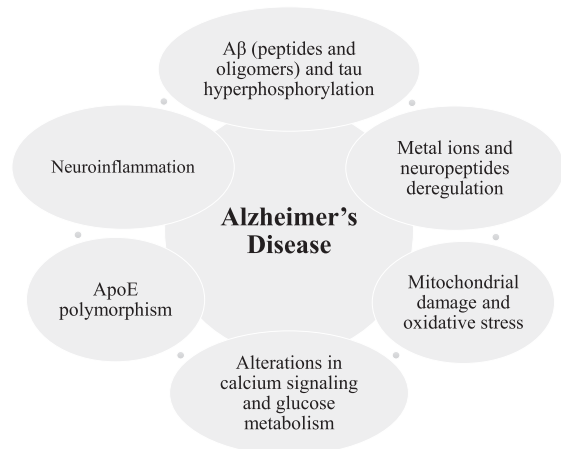

Fig. 1. Summary of Alzheimer's disease multifactorial mechanisms.

than those on incidence. Although a large body of evidence shows a greater prevalence of AD in women [3, 23–31], scientists suggest that this apparent difference is due to an indirect consequence of the greater longevity of females [3, 23, 28, 32, 33]. However, it is not fully clear whether the higher prevalence of AD in women is entirely due to their longer life expectancy, or if other factors put women at greater risk. Although there are reports arguing that the incidence of the disease is not significantly different between the sexes despite increased prevalence [34, 35], a large number of studies have shown higher incidence of AD in women. Some of them demonstrated that AD is three times more common in women than in men [2, 36, 37].

The fact that there are controversial epidemiologic data does not exempt the continuous research on the biological basis of sex differences in AD. Indeed, the biochemical basis for AD-related sex differences is still a gap to be unraveled [38]. The recognition of the relevance of this issue is the strengthening of the debate and the allocation of funds for studies in this theme by the Alzheimer's Association [39]. Thus, the clinical and preclinical studies that will be discussed in the present review bring hypotheses based on a significant body of data stating that sex should be placed as a risk factor for AD predisposition, development, and resilience.

The focus of this review is to highlight the main mechanistic pathways of the sex influence on AD risk. We discuss how changes biased by sex during the development and the aging process could modulate the disease outcome. We also gather the dimorphic pathophysiological mechanisms shown by

the literature in a rationale that encompasses intrinsic factors of both sexes as genetic interactions, hormone influence, and variations in sex-specific biomarkers. Our intention is to unite gaps under an alternative view without disregarding conflicting epidemiological data or controversial results from clinical and pre-clinical studies with animal models. In this context, we find it necessary to make a brief retrospective on this important scientific tool in AD research (see below). These models allow the investigation of pathophysiological mechanisms and the evaluation of potential symptomatic and neuroprotective/preventive therapies.

ADVANCES IN AD ANIMAL MODELS

The use of animal models over the years was very important for AD research. The identification of biological targets with an explicit role in the AD early stages contributes to the development of new therapeutic strategies to alleviate or prevent this neurodegenerative condition [40]. It is important to mention that the pathophysiology observed in animal models may not necessarily reproduce all clinical findings observed in patients and, although there are a wide variety of valid animal models, none of them summarizes all AD aspects [41]. In general, AD animal models comprise non-transgenic (non-Tg)–spontaneous or induced–and transgenic (Tg) models. In addition to humans, few species (dogs, cats, sheep, and nonhuman primates) spontaneously develop amyloid plaques and tauopathies (disorders related to NFT formation) associated with cognitive decline [42–46]. There is a limitation in the use of spontaneous models for experimental research in terms of availability, costs (based on long lifetime), standard techniques, and ethical reasons [40]. Thus, similar to other areas of research, rodents are the most used animal models of AD, despite they do not spontaneously display the histopathological characteristics during aging.

The first AD-induced rodent model was based on the cholinergic hypothesis. This hypothesis suggests that the degeneration of cholinergic neurons, which protrude from the basal forebrain to the neocortex, is an early outcome of the disease [47, 48]. This approach has provided knowledge about learning and memory impairment related to cholinergic neurotransmission, and allowed the assessment of cholinomimetics and acetylcholinesterase inhibitors, the first line of drugs for AD treatment [49–51].

Other AD-induced model comprises the intracerebral or intracerebroventricular infusions of Aβ peptides [52]. Aβ intracerebral infusions cause learning and memory deficits, as well as other behavioral changes similar to those observed in humans [53–55]. The administration of streptozotocin (STZ) is also used to induce an AD non-Tg model [21]. STZ selectively disrupt insulin secreting cells resulting in diabetes mellitus [56]. When administered by intracerebral infusions, STZ induces dysfunctions in the brain insulin system [57], accompanied by behavioral and neurochemical alterations related to aspects of AD.

The identification of several genes and the comprehension of its role in the early-onset familial pathology enabled the production of Tg mouse and rat models for AD. The Tg-mice models were first proposed in the mid-1990s, such as the PDAPP model, followed by the Tg2576 [58] and APP23 [59] (all AβPP-based models). The discovery of mutations in PSEN genes led to the development of PSEN1 and PSEN2 Tg mouse models. Although the aforementioned Tg animals have an increase in the $A\beta_{40}/A\beta_{42}$ ratio, they show few cognitive abnormalities, and lack plaque formation, tau hyperphosphorylated form, and NFT [40]. Tg-mice models of tauopathy were designed to test the development of NFT, in addition to enabling the interaction between NFTs and other aspects related to AD pathology. For example, Lewis et al. [60] have shown increased formation and distribution of NFTs in brain regions vulnerable to the amyloid lesions using the JNPL3 model. P301S Tg-mice, derived from the PS19 line, overexpress the human tau gene with a 5-fold increase compared to endogenous mouse tau. P301S mice also develop synaptic deficits and microglial activation prior to neurodegeneration and NFT [61, 62]. The rTg4510 model rapidly express neuronal loss, spatial memory deficits, and NFTs at an early age [63, 64].

The triple transgenic mouse model (3xTg-AD) was developed in an attempt to overpass or refine the remaining limitations in Tg models. Mice of this Tg strain co-express the human wild-type tau isoform and both PSEN1 and AβPP Swedish double mutations because of the crossbreeding between carriers of these genotypes. Overall, these models replicate elements consistent with the amyloid cascade hypothesis, exhibiting progressive Aβ deposition, cerebral amyloid angiopathy, astrocytosis, microgliosis, hippocampal and synaptic atrophy, neurotransmission dysfunction, and cognitive impairments (for review, see [40, 65–67]). More recently, genetic modifications with the use of viral

vectors have originated several Tg-rat models in which AD-related genes are selectively expressed in brain regions relevant to the disease [68, 69]. As recently reviewed by Do Carmo and Cuello [70], the Tg-rat models are a very good alternative to mice models because of a greater genetic, physiology, and morphology similarity with humans and a better behavioral characterization.

Overall, because it encompasses a variety of the disease aspects, AD Tg models are the most widely used nowadays. Nevertheless, the high cost, the chronological mismatched neurochemical and behavioral changes, and the genetic background of the strain itself are some drawbacks for the use of Tg models, which enlighten the relevance of the research conducted with non-Tg models as well. Both models will be reviewed from the perspective of sex differences in a later section.

EVIDENCE FOR SEX DIFFERENCES IN AD

Human findings

The discrepancies observed in previously discussed epidemiological studies may be due to many factors, such as 1) different AD diagnostic criteria and criteria for excluding other types of dementia; 2) small sample size, statistical power or lack of age groups in the analysis, which could result in inaccurate estimates; 3) type of study (e.g., cross-sectional analysis, prospective or retrospective cohort); 4) cultural differences that could affect the lifestyle over the years; and 5) inclusion/exclusion criteria regarding comorbidities [33]. In a recent study, Viña and Lloret have raised the percentage of people suffering from AD in Europe stratified by age categories. They have shown that the amount of women with AD is higher in all age groups, with the exception of the 65–69 age group [17]. Moreover, epidemiological discrepancies among Europe, Asia, and North America can be attributed to social, cultural, and historical aspects [71]. In Brazil, the annual rate of mortality of people suffering from AD has been higher in women than in men in the last decade [72]. In 2010 and 2014 the Alzheimer's Association published two alerts highlighting the disproportionate number of women who are affected and living with AD [73, 74], particularly those aged 65 years or older, who are twice as likely to have AD compared to age-matched men.

In recent years, there has been a significant advance in the search of the physiological basis for the sex differences in AD. Before discussing them, it is important to highlight the conceptual distinction between sex and gender. Sex is an essentially biological, chromosomal, hormonal trait that relates to reproductive differences between men/male and women/female. In contrast, gender refers to psychological, social, political, and cultural differences between the sexes [75, 76]. In this context, Rocca and colleagues considered three categories of factors related to sex and gender differences in the risk of developing AD. First, there are risk factors that are equally frequent in men and women but have a stronger effect on one sex, for example the APOE genotype (see below). Second, there are risk factors that have similar effect on men and women, but are culturally or socially more common in one gender (e.g., access to education and employment). Finally, there are risk factors restricted to sex (e.g., ovariectomy and abrupt hormonal loss over a period of life). Hence, multiple factors may contribute to the differential incidence and progression of AD between men and women, including sex-related (chromosomal, epigenetic, or hormonal differences) and gender-related (psychosocial and cultural differences) factors [77].

Apolipoprotein E (ApoE), involved in the cholesterol transport, favors Aβ aggregation and the enhancement of amyloid plaques [78–81]. There are three major isoforms of the ApoE protein (ApoE2, ApoE3, and ApoE4), encoded by three alleles of the ApoE gene (E2, E3, and E4, respectively). Carriers of an E4 allele are three to four times more susceptible to AD compared to non-carriers [82, 83]. The presence of this allele decreases the age of the disease onset in a manner dependent on the number of alleles and sex [84, 85]. For example, women with one or two E4 alleles are at higher risk than men with the same genotype in the age group up to 85 years [86]. Women with E4 also show more significant changes in the connectivity pattern of the neural network [87], more presence of tauopathy [84] and a stronger association between tau and APOE [88], reduced brain metabolism and increased brain atrophy [89], and worse memory performance than men [90]. Moreover, postmortem studies showed exacerbated deposition of amyloid plaques and NFT formation in the brains of E4 allele carriers [91, 92] and the E4 effect on AD biomarkers in the cerebrospinal fluid is more pronounced in women than in men [93]. Recently, a meta-analysis study reported the age-dependency of ApoE4 as an AD risk factor for women, being restricted to an age range of 10 years

[94]. Other genetic predictors have been identified as sex-specific for AD. For example, Karch & Goate reviewed 20 genetic loci on autosomal chromosomes that are linked to increased risk of AD [95] and some of them, as Serpin genes, showed stronger association with amyloidosis, especially among females [88]. However, the fully role of such genes on AD sex differences requires further research.

The ApoE E4 genotype may also interact synergistically with alcohol consumption, smoking, physical inactivity and high saturated fat intake [96, 97]. These factors can trigger metabolic syndrome, characterized by obesity, insulin resistance, hypertension, and dyslipidemia, factors that have also been associated with an increased risk of AD [98]. As mentioned, reduced cerebral glucose metabolism is common to insulin resistance (type 2 diabetes) and AD, and it has been implicated in increased $A\beta$ deposition, tau protein hyperphosphorylation, vascular dysfunction, and inflammation [99–101]. Thus, these interactions may explain the differential effects of ApoE between men and women, as they differ in their exposure to smoking, alcohol consumption, food preferences, and physical activity [77].

Gender-related factors as educational level can interact with the effects of ApoE E4 genotype. In fact, women carrying the E4 allele, but with early high educational level have reduced risk of dementia [102]. In addition, individuals who perform mind stimulator activities, those requiring complex interactions with data and people, have lower risk of dementia [103]. Educational level, type of occupation during working life, and cognitively stimulating leisure activities during the middle age are part of an intellectual enrichment that may delay the cognitive decline and dementia onset [104, 105]. Leisure activities throughout life, education, and mental stimulation as part of labor are primarily gender-related and historically contingent. Indeed, men historically have higher educational attainment than women, and in some regions of the world, especially in underdeveloped and developing countries, this discrepancy is still considerable [106]. Likewise, jobs that are cognitively more demanding have been historically restricted to men (e.g., directing public or private institutions, serving high-level political roles, holding high academic positions, etc.), although in a few countries this pattern has become more equal between genders [71, 107]. In this sense, the changes in social and cultural attitudes that have been occurring in many countries over the past decades may alter future projections of gender influence on AD [108].

Finally, there are some factors restricted to sex, such as ovariectomy in women, which may be associated with an increased risk of developing AD. Research has shown that women who had bilateral ovariectomy before menopause had an increased risk of cognitive decline and dementia [77]. Bove and coworkers reported the results of a cohort study on the association between surgically induced menopause, cognitive decline, and AD. Early menopause was associated with a faster decline in cognition, specifically on episodic and semantic memories, and enhanced amyloid plaques formation in AD patients. The authors also demonstrate that estrogen replacement therapy in a perimenopause stage was associated with a slower cognitive decline [109]. Thus, it is suggested that early bilateral ovariectomy in women causes an abrupt decline in estrogen levels which might mediate a chain of reactions leading to degenerative and cerebrovascular lesions. Estrogen-related factors will be further discussed in this review. Sex differences in human AD studies are corroborated by preclinical studies with animal models, as described below. In general, the human studies discuss direct (AD prevalence/incidence and ApoE genotype) and indirect (educational and hormonal status) features related to sex differences with AD (see Table 1).

Studies in animal models

Table 2 summarizes the variety of AD animal models that considered sex as an independent factor in the experimental design. Most animal studies that have addressed sex differences in AD used Tg models, and, to our knowledge, there are very few studies with non-Tg animals using both sexes. For example, only two studies have recently verified the influence of sex on the STZ model. Biasibetti and colleagues [110] demonstrated that the behavioral effects and changes in neurochemical markers depended on sex and were more prominent in males. Similarly, Bao et al. [111] showed that females were more resistant to the learning and memory impairment induced by STZ administration. Spatial memory was strongly affected in $A\beta$PP/PS1 Tg-females while spared in males, at all ages. The reduction of the synaptic connectivity and the high density of hypertrophic astrocytes were associated with the memory impairment [112]. Also in the $A\beta$PP/PS1 Tg model, Wang and coworkers reported significantly increased $A\beta_{40}$ and $A\beta_{42}$ levels in the brain tissue of females compared to males at 4, 12, and 17 months. Moreover, at

Table 1
Overview of the features related to AD sexual differences in animal models and human studies

	Features	Sexual differences	References
Human studies	AD prevalence and incidence	♀ > ♂	[2, 3, 23–31, 36, 37]
	Susceptibility to ApoE4 genotype	♀ > ♂	[82, 84, 86, 87, 89, 90, 94, 95]
	Educational enrichment	♀ < ♂	[71, 77, 106–108]
	Ovariectomy	Restricted to ♀	[77, 109]
Animal models	Life expectancy regardless sexual genotype	♀ > ♂	[83]
	Aging-related gene expression changes	♀ > ♂	[124]
	Susceptibility to ApoE4 genotype	♀ > ♂	[118, 119]
	AD histological hallmarks and behavioral deficits	♀ > ♂	[113–117, 120]

> or < indicates which sex is most likely to exhibit or suffer from the listed feature.

Table 2
AD animal models that mostly considered sex as an independent factor in the experimental design

AD animal models		Sex as an independent factor	References
Transgenic	AβPP	+++	[38, 83, 115–117, 258, 278]
	AβPP/PSEN1	++	[112–114]
	Tau	++	[60, 62, 64]
	AβPP/Tau	+	[60]
	3xTg-AD	+++	[82, 120, 189, 297]
	ApoE4	++	[118, 119]
Non-transgenic	Spontaneous	–	?*
	Induced	+	[110, 111]

The signs denote the number of studies using the type of animal model mentioned. *No studies that concomitantly used both sexes in the experimental design was found.

the ages of 12 and 17 months, the load of amyloid plaques was substantially higher in females than in males (at four months of age there were no deposits). Interestingly, the animals presented differences in Aβ levels between the sexes prior to what would correspond to the menopause period in women (at the age of 4 and 12 months). In addition, the relatively unchanged proportion between Aβ species (40/42) at 12 and 17 months for both sexes indicates that sex probably affects only the AβPP overproduction but not the Aβ generation [113]. Recently, a study also showed that in AβPP/PS1 mice the $Aβ_{40}$ and $Aβ_{42}$ levels do not differ between the sexes until nine months of age. After this, there was an increase in plasma amyloid levels in females and a reduction in males [114].

Other studies with Tg mice models (APP23 [115, 116], Tg2576 [117], and AβPP/Tau [60]) observed similar patterns. These studies found that females had higher Aβ levels in several brain regions, more deposition and amyloid plaques formation, as well as a more remarkable neurodegenerative profile when compared to males of the same age [113, 117]. Raber and colleagues showed that Tg female mice expressing human ApoE4 were more susceptible to learning impairments in the water-maze test [118]. Further, Cacciottolo et al. [119] showed stronger Aβ burden

in ApoE4 females than in males. Likewise, in the 3xTg-AD model, female mice exhibited pronounced impairments on learning and memory than males in the water-maze and inhibitory avoidance tasks. However, in the novel-object recognition task there were no sex differences. It is important to note that in this study, in all age groups, no significant difference in Aβ and tau levels was detected [120], contrary to what was observed in the above-mentioned studies. Regarding models of tauopathy, rTg4510 female mice have more severe spatial memory deficits associated with an increased level of hyperphosphorylated tau [64]. JNPL3 female mice exhibit faster tau pathology, and have tau overexpression two times higher than males [60]. On the other hand, mitochondrial dysfunction is greater in male P301S mice at older age [62]. Interestingly, pharmacological treatments that target anti-Aβ actions have differentiated (even opposite) effects between the sexes in Tg mice [121], which reinforces the thesis that sex has to be taken into account in the analysis of studies using AD models. Although the development of Tg models has optimized and tackled unanswered questions, some intrinsic limitations such as the higher amyloidogenesis in females can generate more variable results. Dubal et al. [122] scrutinized how surpass these limitations, and proposed guidelines to choose those

that best embodies the human condition for future research.

The mechanisms underlying the sex differences in AD are not completely understood. Recently, Broestl et al. [83] designed a remarkable experiment to investigate the effects of sex chromosomes and gonads on AD pathology using an AD Tg mice model (overexpression of AβPP). Even though depletion of gonadal hormones is a key aspect of human aging, these same steroids remain relatively stable in older rodent models [122]. To overcome this limitation, the authors depleted the hormones of mice manipulated to have female sex chromosomes, but male sex organs (testicles), as well as male sex chromosomes together with female sex organs (ovaries). Mice with male genotypes died faster regardless of whether they had male or female sex organs. This outcome suggests that sex chromosomes contribute to AD-related brain disorders in AβPP mice.

Finally, Rae and Brown [123], in an extensive review, drew attention to the genotype and sex-dependent differences in lifespan, which have important implications for designing experiments using AD Tg mice models. These authors discussed the need to standardize age-related disorders in these models in order to equate each genotype and sex with different life expectancies. Indeed, the expression profile of some genes in the hippocampus revealed differences in the development of aging-related alterations between male and female brains, which may help to clarify early changes in female brains at risk for AD. For example, in female mice brains, 44.2% of the genes underwent significant change between six and nine months of age, and two thirds of them were downregulated. In contrast, in male mice brains, only 5.4% of the genes were significantly altered during the same period. In subsequent age groups, the changes in female mice brains were much smaller (10.9% from 9 to 12 months and 6.1% from 12 to 15 months) while in the male mice brains most of the changes were related to gene upregulation between 12 and 15 months. Thus, male and female mice brains seem to follow markedly different aging paths and particularly female brains undergo age-related changes much earlier than males [124].

SEX-RELATED FACTORS IN AD

Both human studies and animal models have highlighted the importance of addressing the differences between the sexes in AD pathophysiology. In general,

they showed that females are more susceptible to the disease-related features (Table 1). In this respect, it is important to mention that susceptibility and vulnerability are different concepts when considering sex-specific physiological factors involved in AD (see below). According to Kottow [125], susceptibility is a feature of subjects who have *a priori* disadvantages and are at risk of suffering other damages. On the other hand, vulnerable subjects would not present those disadvantages, but are at risk of damage provided a certain condition affects them. In other words, knowing that susceptibility indicates a prior weakness not yet established, but with risk of development, and vulnerability refers to the weakness already present, but with less resilience, it is possible to draw a comparison between morbidity and mortality with these concepts. Indeed, mortality means the proportion of deaths among those who may die, and morbidity the proportion of ill patients among those who may become ill. Thus, the idea of vulnerability is closer to the concept of mortality, and that of susceptibility to morbidity. Taking this into account, both conditions (i.e., susceptibility and vulnerability), when expressed differentially between the sexes, may skew the course of the disease in terms of morbidity and mortality. The view of greater vulnerability of men to the disease is congruent with previous reports. For example, one of the strongest predictors for aggressive disease course and progression to death following a diagnosis of AD is male sex [122, 126]. On the other hand, men have better overall health at older ages than their female counterparts in terms of morbidity, but not mortality [127].

Otherwise, the idea of increased susceptibility to AD by females while a greater vulnerability in males is questionable since females would be more resilient in earlier stages of the disease as shown by some studies [128–131]. Indeed, these studies show a greater resilience of females due to protection at low levels of AD pathology [131] or an advantage of cognitive reserve [128–130]. However, the evaluation of female's resilience using only a single cognitive demand (i.e., verbal memory) may bias the issue, especially when studies have shown there is baseline advantage of females over males in verbal memory [132], which may hinder generalizations for the pathology as a whole. Moreover, other studies counteract these data by stating that females may be more sensitive to AD-related pathological agents and experience greater and more rapid structural loss than males. Thus, males would be more resilient because they have greater cognitive reserve [71].
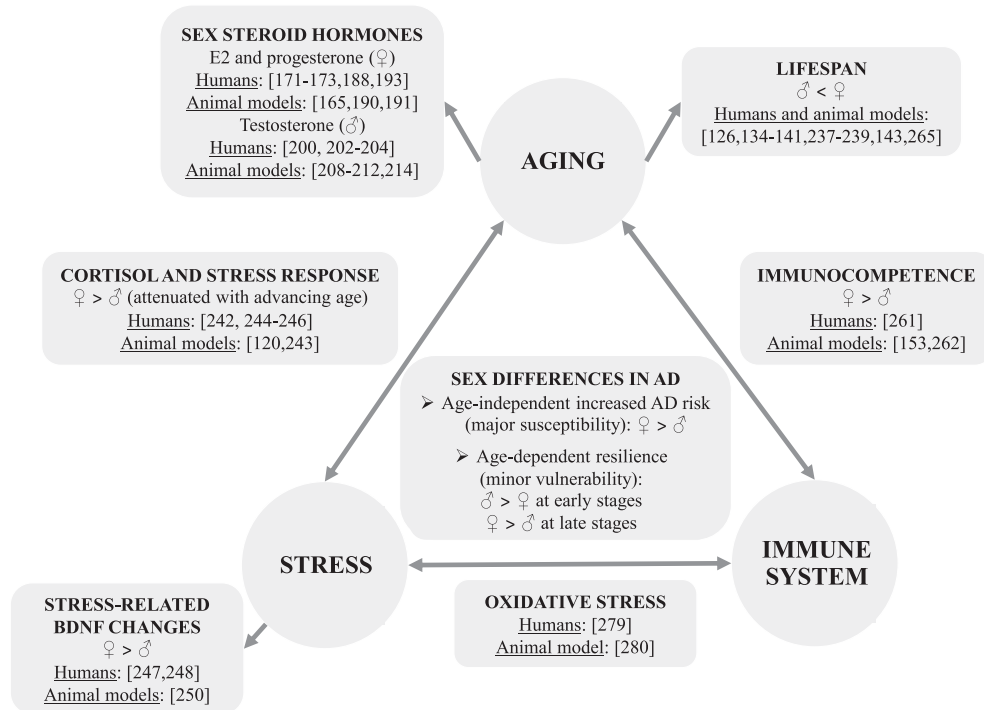
Fig. 2. Integrative view of the main factors involved in AD sex differences. Data reveal substantial differences in the overall age-related changes between the brains of males and females. Aging-related components as sex hormones, stress response and the immune system seem to be involved in sex-specific brain predisposition to AD. Besides genetic factors that enhance the AD susceptibility of females, developmental changes linked to sex-specific and stress hormones directly bias females to increased AD risk. The sex-biased risk for AD in which females appear to be more susceptible to the disease raises the questions: If one sex is more susceptible, is it necessarily more vulnerable? Could the intrinsic factors linked to sex from early development to the natural aging process lead to different neuropathology processes between the sexes? Susceptibility appears to be greater in females than in males and this does not appear to be age dependent. Conversely, the vulnerability to comorbidities or intrinsic AD factors seems to be age dependent. A pattern showing that females would be more vulnerable at early ages and males would be more vulnerable at more advanced stages of the disease highlights the highest mortality rate of this sex in AD.

From another perspective, age seems to be a key part in this discussion. Fisher et al. [33] argued that imprecise timing of pre-AD diagnosis may make the definition of age-of-onset more variable. For example, women receive the diagnosis of AD later than men. Other caveat pointed by the authors is that the use of clinical diagnosis may categorize other dementia presentations incorrectly as being AD. In this respect, sex and gender factors interact with age across development to alter risk for dementia. Brain sexual dimorphism begins in pregnancy and may promote risk or resilience on the disease outcome across the lifespan. Interestingly, males have a higher potential risk for the development of other types of dementia excepting AD, such as vascular dementia, Lewy body dementia, dementia associated with Parkinson's disease, dementia due to frontotemporal degeneration, or by multiple causes [133]. Regarding AD-type dementia, a systematic review [71] endorsed several findings that have pointed to a shorter lifespan among males [134–140], regardless of age at diagnosis [141]. Therefore, sex differences in the clinical manifestations of the disease may vary across the cognitive diagnostic spectrum, and additional longitudinal work is needed to better understand this dynamics process [142].

Furthermore, it is difficult to conclude whether the observed sex differences is driven by differences in the AD etiology, or simply by differences in risk factors during brain aging, such as the higher proportion of comorbidities and mortality in men or greater disability but longer survival in women [135]. The overview of mechanistic processes related to aging and addressed in this section will be discussed under the integrative rationale outlined in (Fig. 2), which shows factors intrinsic to sex and involved in the relative sex susceptibility and vulnerability to AD.

Sex hormones

Numerous physiological and behavioral effects of estrogen (E2) have been the focus of preclinical and clinical research. The role of E2 goes far beyond the effects on sexual differentiation and reproductive function. The drastic reduction of E2 levels is a key feature of menopause, with negative consequences to the female organism, such as on bone density and cardiovascular functioning [143, 144]. The effects of E2 on these peripheral systems are well documented, as well as the important role of this hormone on the central nervous system [145–147]. For example, as reviewed by Galea et al. [148], E2 can increase neurogenesis in several brain regions, such as the dentate gyrus in the hippocampus, which contributes to learning and memory mechanisms. In animal models, E2 has shown a neuroprotective effect by increasing dendritic spines in the hippocampus [149], LTP upregulation [150], modulation of several neurotransmitter systems [151], and decrease in cell death by modulating mitochondrial functions [152]. E2 is also responsible for increased immunocompetence in females [153, 154]. Likewise, E2 positively regulates the expression of antioxidant enzymes, as shown by increased levels of reduced glutathione [155], which could preserve the immunologic function throughout the aging process [153, 156–158].

Paganini-Hill and Henderson [159] reported that the marked E2 decrease during menopause contribute to the AD pathogenesis. Indeed, evidence show that E2 has a beneficial role against several dysfunctional brain systems associated with AD [160, 161]. For example, E2 can reduce Aβ levels by 1) favoring the non-amyloidogenic pathway by MAPK/ERK activation and reduction of BACE levels; 2) promoting Aβ clearance by microglial phagocytosis; and 3) regulating enzymes involved in Aβ degradation such as neprilysin (NEP) [162]. E2 also prevents the neuronal loss mediated by Aβ toxicity, and activates the anti-apoptotic Bcl-2 protein at the same time it suppresses the expression of the proapoptotic isoform [163]. Moreover, E2 decreases hyperphosphorylated tau levels, and this effect depends on the activity of kinases and phosphatases, such as GSK-3β, Wnt, and PKA [164]. E2 depletion leads to Aβ accumulation in the Tg2576 mice brain, which can be reversed by hormone replacement [165]. However, ovariectomy in females did not alter Aβ brain levels, but significantly reduced AβPP levels [166]. On the other hand, although E2 treatment reduced Aβ brain levels, AβPP levels did not change in another study [167]. Together,

both studies suggest that E2 possibly influence the AβPP processing, Aβ levels, or its deposition.

Several epidemiological studies and clinical trials have suggested that the E2 replacement reduces risk of AD in healthy women, delays disease onset, and improves cognitive function in women with AD [168–173]. In addition, women with AD presented lower serum levels of E2 [172]. On the other hand, some authors have refuted the efficacy of E2 in AD patients [173–175]. In addition, some studies have indicated that E2 replacement is not beneficial for AD, especially when the disease is already in course [176, 177]. Others have shown increased risk for cardiovascular disease, dementia, and decreased brain volume in women aged 65 to 79 years as a consequence of this replacement [178–180].

In face of this controversy, studies need to address multiple factors that can modulate the hormonal response in AD research [176]. For example, the studies that investigated the potential neuroprotection exerted by E2 in women have led to the hypothesis that this action only occurs in the time window called perimenopause [77, 181]. Perimenopause is a natural transition towards menopause, during which there is a sharp decline of hormone levels, especially estrogen and progesterone [182, 183]. This transition is considered a critical period to the potential neuroprotective effects of E2 [184, 185]. Another inherent problem that may result in inaccuracies is the fact that there is still no appropriate model that naturally mimics human hormonal conditions (e.g., menopause; for review on caveats and alternatives, see [122]).

Moreover, the bioavailability of E2 may influence its actions on the central nervous system. A recent study by our research group using the scopolamine-induced amnesia rat model has shown that E2 administration resulted in a bimodal effect. Specifically, although the acute treatment with E2 counteracted the scopolamine-induced acquisition impairment, E2 impaired the consolidation process in female with low physiological levels of the hormone. Differences in E2 bioavailability can activate genomic and non-genomic actions during the different phases of memory (acquisition and consolidation) and the interaction between these two pathways possibly interfered with the behavioral outcome [186]. Both the long lasting genomic and the rapid non-genomic pathways participate in the activational and organizational effects of E2 on physiological and behavioral processes [187]. From this perspective, the developmental and physiological differences between sexes, particularly regarding the activational

and organizational effects of the sex steroid hormones, could contribute to the sex-related AD framework. As recently reviewed by Pike [188], the sex-specific activational variations during aging, combined to differences in the sex hormones organizational actions during early development may confer inherent vulnerability to the female sex.

In addition to E2, other sex steroid hormones such as progesterone and testosterone may also be involved in the AD sex differences. For example, recent work has demonstrated that the protective efficacy of E2 in non-Tg and AD Tg rodents is regulated by progesterone [189–191]. Progesterone have also shown neuroprotective actions against AD, such as gamma-secretase modulation [192] and increased Aβ clearance by insulin degrading enzyme [191]. In addition, studies in cell cultures, animal models, and humans have shown that progesterone also modulates tau protein phosphorylation [193]. Unlike E2, progesterone had no effect on alpha-secretase [192, 194]. However, a study showed that the administration of progesterone in ovariectomized rats induced a downregulation of beta-secretase gene expression [195]. Progesterone administration also promoted better performance in novel-object recognition and T-maze tasks in a Tg mice model of AD [196]. In this same work, progesterone administration not only significantly reduced Aβ levels, but also synergistically increased the E2 neuroprotective action. In contrast, continuous progesterone treatment did not alter Aβ levels and eventually inhibited the E2 protective effects in another study [190]. Finally, progesterone significantly attenuated oxidative damage resulting from glutamate- [197] and Aβ-induced [198] toxicity in hippocampal cell cultures. In summary, there is evidence of a role of progesterone in the neuroprotective action of sex steroids.

The aging-related loss of androgens also has consequences to the brain. In human studies, aging-related loss of androgen has been associated with increased risk of developing AD. For example, AD men have lower circulating [199, 200] and brain testosterone levels [201, 202] compared to men without AD. Brain testosterone levels were also inversely related to the Aβ levels in men who developed early-onset AD [202]. Overall, the loss of testosterone associated with aging seems to precede the AD clinical diagnosis, suggesting that androgen depletion can be a precursor event that contributes to the disease onset [202]. Moreover, low testosterone levels agreed with increased formation of the amyloid plaques [203],

lower cognitive performance [200], and reduced brain metabolism [204]. Some studies have also shown that testosterone treatment improves cognitive function in men [205, 206]. In a male reproductive aging rat model, cerebral decrease of dihydrotestosterone occurred concomitantly with increasing levels of Aβ$_{40}$ during aging [207]. Furthermore, androgen depletion by orchiectomy significantly accelerated cognitive deficit and brain injury in 3xTg-AD mice [208]. In APP23 mice, the genetic manipulation of aromatase, resulting in increased testosterone bioavailability, led to a significant reduction of the AD pathology and consequent improvement of the cognitive function [209]. Androgens also protect the brain against a variety of AD-related insults. For example, testosterone may protect against Aβ toxicity [210–212], oxidative stress [213], and tau protein hyperphosphorylation [214]. The neuroprotective effects of testosterone may be related to its action at the androgen receptor, or to the conversion to E2 by aromatase [213, 215].

The loss of sex steroid hormones during aging is undoubtedly one of the mechanisms related to AD sex differences. Although each sex-specific hormone has a potential neuroprotective relevance to AD risk, female hormones present a more abrupt decline and, therefore, the susceptibility to AD would be higher in women. Conversely, men would be less susceptible to the loss of estrogen-mediated neuroprotection, but they might present greater vulnerability to other AD-related factors (Fig. 2).

Cortisol/corticosterone

Long-term glucocorticoid overload during chronic stress leads to changes in the hippocampus [216, 217], including dendritic remodeling [218], LTP reduction [219, 220], increased oxidative stress [221], and reduced hippocampal volume [222]. Chronic stress also alters the dendritic morphology of the prefrontal cortex neurons [223, 224] and suppresses neurogenesis in the dentate gyrus [217, 225], and this effect increases with aging [226]. The consequences of the functional changes mentioned above result in cognitive impairment, particularly of hippocampus-dependent memories (see [227] for review) and executive functions [228].

Of note, there is an increase in cortisol levels in both plasma and cerebrospinal fluid of AD patients. This increase is positively correlated with the degree of cognitive impairment [229], but not to the co-morbid depression symptoms of the disease

[230]. In addition, a longitudinal study demonstrated that stressful life-long events are associated to an earlier onset in familial AD [231]. It is noteworthy that AD patients exhibit functional alterations in the hypothalamic-pituitary-adrenal axis (HPA) [232–234]. In addition, AD patients with high cortisol levels have worse performance in memory tasks compared to those patients with lower levels [235]. These patients are unable to adequately cease stress responses, leading to a chronic HPA axis hyperactivity and deleterious effects on the aging brain [236].

Females live longer than males in a wide variety of animal species, including humans. Behaviors like the search for food and the risk taking are rather traits of males than females in most mammals species [237], which contributes to the increased male mortality in all ages [238, 239]. As cortisol or corticosterone is inversely associated with risk behaviors [240], plasma concentrations of stress-related hormones are considerably higher in adult females than in males [241]. On the other hand, some authors have described an aging-related decrease in cortisol levels only in women [271, 272]. Similarly, 3xTg-AD female mice presented decreased corticosterone levels compared to age-matched males, while adult females of non-Tg mice had a six-fold increase in basal plasma corticosterone compared to adult males [243]. Thus, although sexual dimorphism to stress hormones is present across life, it seems to be attenuated with aging in humans and animal models.

In humans, a large meta-analysis by Otte et al. [244] showed that the effect of aging on the cortisol response to pharmacological or psychological stressors was almost three times higher in women than in men. The size effects of some studies that controlled the sex hormones variations in women (e.g., standardization of menstrual cycles, exclusion of women using oral contraceptives or hormone replacement therapy) did not differ from the size effects of those who did not. This suggests that sex hormones did not appear to alter the effect of aging on the stress response in women. In agreement with this finding, studies that examined the effect of stress on cognition in older men and women found that acute psychosocial stressors caused memory impairment only in women [245, 246]. In other words, even with the attenuation of the differences in cortisol levels across aging, the stress response still triggers more harmful effects in females. Thus, the stress response is another AD risk factor that confers greater susceptibility to this sex (Fig. 2).

In addition to cortisol response per se, the association between stress and BDNF is another mechanism by which women may be more susceptible to AD. A meta-analysis comprising intercontinental studies found that the BDNF Met66 polymorphism, linked to lower BDNF transport, was associated with AD increased risk in women, but not in men [247]. Similarly, in a study with young adults, women with the BDNF Met66 polymorphism showed an increased cortisol response to a social stressor, while the same polymorphism was associated with a decreased cortisol response in men [248]. In addition, BDNF was decreased in cortical areas of both sexes, but BDNF was downregulated in the entorhinal cortex only in females, indicating that BDNF may be a female-specific risk gene for AD [249]. In mice, stress reduces hippocampal BDNF levels in females, but not in males [250].

In animal models of AD, stress causes deficient AβPP processing, which leads to increased Aβ_{40} and Aβ_{42} levels in the hippocampus [251], increased tau protein phosphorylation in the hippocampus and prefrontal cortex [252], as well as enhanced cognitive impairment [253]. Interestingly, these effects occurred only in stress-susceptible animals, and not in the stress-resistant ones [254], suggesting that stress actions on the nervous system require vulnerability to these effects. Some evidence suggests that sex-biased signaling in corticotropin-releasing factor increase molecules associated with AD pathogenesis, suggesting that stress may be a risk factor especially in women [255] and female mice [256]. In addition, treatment with a synthetic glucocorticoid (dexamethasone) potentiated the disease-related damage in 3xTg-AD mice [257]. Furthermore, AD Tg mice showed HPA axis hyperactivity that was dependent on age and sex [258]. For example, Clinton et al. [120] found that 3xTg-AD nine-month-old females had higher stress-induced corticosterone response in comparison to 3xTg-AD males and to age-matched non-Tg females. This differential stress response was not apparent in fifteen-month-old animals, along with the cognitive disparity between the sexes. It is possible that cognitive sex differences in stressful tasks exist only when females have increased stress response compared to males, regardless of genotype. The authors raised the possibility of a progressive synergistic effect between increased stress response and the AD pathology [120]. A possible role for stress response in AD sex differences is illustrated in (Fig. 2). As mentioned above, the stress-related features are more likely to participate in sex differences

to AD risk earlier in life than during aging, when the sex differences regarding stress response are attenuated.

The immune system also plays an important role in the relationship between stress response and aging, and thus might be an important factor to explain sex differences in AD, as illustrated in (Fig. 2). The hypercortisolemia caused by HPA hyperactivation in AD patients [259] could result in peripheral immunosuppression [260]. Furthermore, the literature indicates that the immune system in females works more efficiently and for a longer period than in males [261] and shows stronger humoral [262] and cellular responses [156]. Thus, the sexual dimorphism in the immune response indicates that females could be more resistant to infections [263, 264], and males would be more vulnerable to diseases. Particularly in AD, the systemic immune changes exhibited by immunodeficient subjects may be causally related to increased AD pathology [243]. Thus, despite females would be more susceptible to AD—due to the genetic and developmental factors described throughout this review—males could be more vulnerable due to the difference in immunocompetence.

This view is illustrated in (Fig. 2), in an attempt to integrate all the sex differences discussed above that possibly underlie the greater AD prevalence in females. In short, the exacerbated stress response (mainly earlier in life) and the sharp decline in sex hormones levels during aging render females more susceptible to AD. In parallel, the less effective immune function in males and their shorter lifespan could confer more vulnerability to this sex once they develop AD. Some authors have already strengthened this hypothesis pointing out the higher vulnerability of male immune system which results in an increased mortality in AD male mice [243] and men [265].

NEUROCHEMICAL AND MOLECULAR FACTORS

Oxidative stress

Oxidative stress and metal levels in the brain are other mechanisms closely related to AD (Fig. 1). For example, high ion metal levels in the brain such as copper (Cu^{2+}), zinc (Zn^{2+}) and iron (Fe^{3+}) may facilitate Aβ precipitation [266, 267]. The catalytic activity of Aβ reduce Cu^{2+} and Fe^{3+} [268] and this process may be the main source of reactive oxygen species (ROS) that provoke oxidative damage and neurodegeneration in brain regions affected by AD

(see [269] for review). Furthermore, abnormalities in metal homeostasis have been shown in AD brains, such as increased levels of Fe^{3+} and Zn^{2+} [269, 270] and decrease in Cu^{2+} levels [271–274]. In addition to these metals, AβPP overexpression resulted in significantly increased manganese (Mn) levels in the brain of AD Tg mice [274, 275]. Moreover, the Cu^{2+} deficiency observed in both AD human [271–274] and Tg mice [116, 275, 276] can be a direct consequence of the AβPP/Aβ overproduction [275]. Indeed, Cu^{2+} binding Aβ domains and AβPP N-terminal region interfering in the AβPP/Aβ metabolism [275]. Thus, such deficiency could secondarily facilitate the Aβ accumulation and amyloid plaques formation [116, 276].

Interestingly, brain oxidative stress parameters in AD seem to be distinct between sexes [277, 278]. For example, Viña and Lloret [17] discuss the role of mitochondrial mechanisms on the higher incidence of AD in women. Conversely, male AD patients have a reduction of the glutathione concentration in red blood cells when compared to female AD patients as well as healthy age-matched controls. The authors suggested that a decrease in the concentration of glutathione, the major antioxidant in cells, should render men more vulnerable to AD [279]. In addition, it is possible to observe lower levels of reduced glutathione in spleen and brain cells of male mice, which indicates an increase in oxidative status in males relative to females [280].

In the same context, metal levels could be related to sex differences in AD. Studies have shown that Cu^{2+} levels are lower in female mice, whereas cobalt (Co) levels are higher, especially in older animals [278]. Moreover, Mn levels exhibit marked sex differences with consistently higher levels in females compared to males [278]. Sex and age differences in Cu metabolism or in Cu-mediated toxicity have also been reported in rats [281–284]. From these findings it is possible to infer that in humans there might be differences in oxidative stress related to Cu homeostasis between sexes, which could differently influence AD progress [278]. Zn^{2+} also contributes to the Aβ aggregation, characterized by high Zn levels in amyloid plaques [285]. Lee et al. [286] showed that mice with lower expression of the Zn transporter had lower amyloid plaque formation and higher Zn levels correlated significantly with $Aβ_{40}$ and $Aβ_{42}$ levels. This work also demonstrated that the sex difference in Zn^{2+} levels at the synapses contributes to the discrepant amyloid plaque formation in Tg2576 mice. Females expressing higher Zn transporters had more
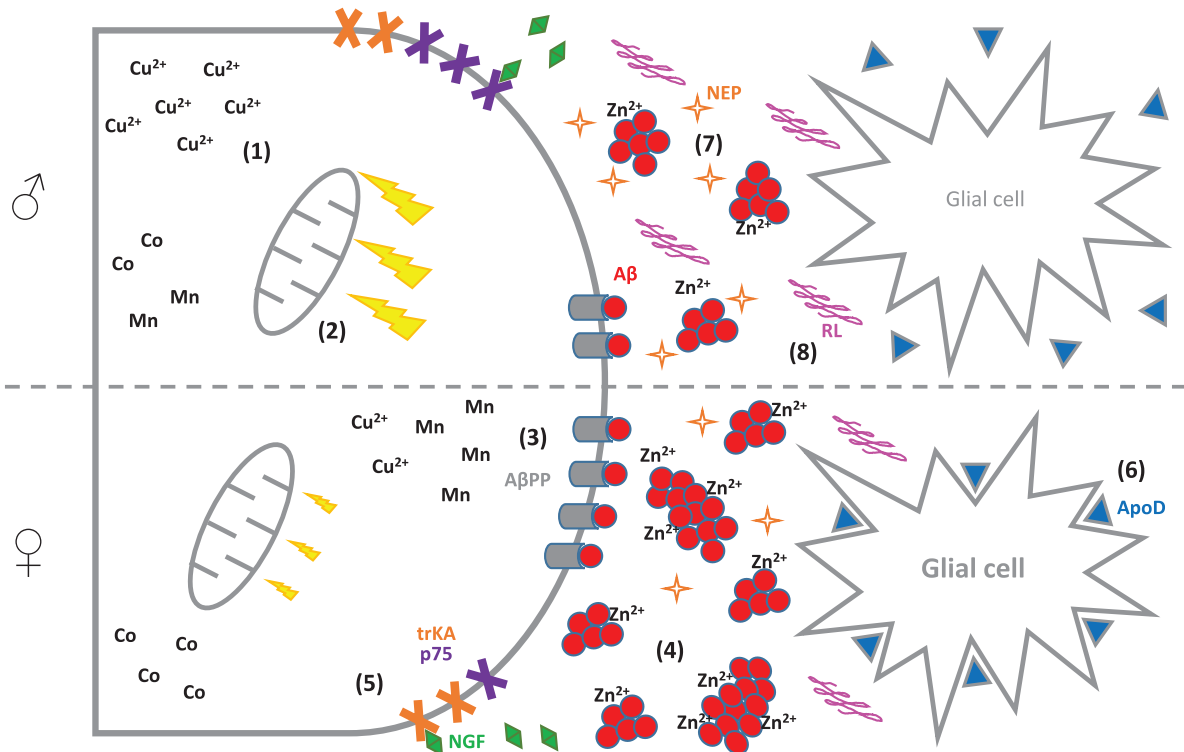
Fig. 3. Schematic representation of the possible interactions between the main neurochemical and molecular factors associated with aging and AD sex differences. (1) The catalytic Aβ ability to produce Cu^{2+} is a source of reactive oxygen species (ROS) that provoke oxidative stress and neurodegeneration (Perry et al. [269]). In aging male subjects, Cu^{2+} levels increase Aβ aggregation and oxidative stress (Maynard et al. [275, 278]) and (2) AD male subjects have increased mitochondrial dysfunction (Dumont et al. [62]) and oxidative stress because an antioxidant levels reduction (Liu et al. [279]; Viveros et al. [280]). (3) AβPP overexpression in females (Wang et al. [113]) significantly increases Mn levels at the same time as reduce Cu^{2+} levels (Maynard et al. [278]). Moreover, (4) amyloid plaques have high Zn^{2+} levels and Zn^{2+} contributes to the aggregation [286]. Lee et al. [287] showed that females have more plaques compared to the age-matched males and older females have higher Zn^{2+} levels than males. Although (5) the supply of NGF receptors is higher in males due to more pronounced reduction in AD female subjects [288], the same proportion of the high-affinity trkA receptors in both sexes could offset the greater loss of low-affinity p75 receptors in females maintaining the neurotrophic signal. At the same time, (6) ApoD neuroprotective actions induce glial activation and scavenging properties surrounding the amyloid plaque formation [291]. The ApoD increase only in healthy aging women may be a result of the early need for their neuroprotective actions on the inflammatory response to some stressors (e.g., Aβ oligomers and fibrils initial production), but may also indicate a delayed ApoD protective response in men. Meanwhile, (7) NEP decreased more prominently in female than male transgenic mice [297], which facilitate Aβ deposition. Finally, (8) RL could also be involved in the AD sex differences with lower expression in female animals [311]. Cu^{2+}, ion cooper; Co, cobalt; Mn, manganese; Zn^{2+}, ion zinc; AβPP, amyloid precursor protein; Aβ, amyloid-beta peptide; ApoD, apolipoprotein D; NGF, neurotrophic growth factor; RL, reelin; NEP, neprylisin.

plaques compared to the age- and genotype-matched males and older females had higher Zn^{2+} levels than age-matched males. However, animals with lower Zn transporter did not present sex differences in Aβ deposits. In another study by Lee et al. [287], changes in E2 levels affect the brain Zn^{2+} levels in the synaptic vesicles, so that ovariectomy increased brain Zn^{2+} levels and E2 replacement reduced those levels. In view of the evidence above, changes in Zn^{2+} levels in senescent animals may contribute to the AD sex differences. However, they fail to explain the differences in the Aβ processing that is already evident in young animals [38]. New studies should focus on

the interaction between the aging process, changes in Zn^{2+} levels and the AD pathogenesis.

Figure 3 illustrates the suggested interactions between oxidative stress, metal alterations, and other molecular factors (see below) that may encompass a differential cascade of events associated with AD sex differences. AβPP overexpression [113], and the increased burden of amyloid plaques associated with high Zn^{2+} levels [286], reinforce the idea of more AD susceptibility in females. Furthermore, the increased oxidative stress due to high Cu^{2+} levels in aging male subjects [275, 278] and the reduced antioxidant levels [279, 280] emphasize the weakening of the male

defense network against toxic substrates, which is accordance with the shorter lifespan in males discussed previously.

Other molecular factors

Among other possible factors that might be involved in AD sex differences there are the AMPA glutamatergic receptors and the cognate receptors of the neuronal growth factor (NGF) related to neuronal survival, such as trkA and p75 [288]. These receptors were analyzed in the nucleus basalis of healthy, mild cognitively impaired, and mild/moderate AD patients of both sexes and the results showed that they go through a sex-dependent differential shift during the progression of the disease. Patients with AD of both sexes present less high-affinity trkA receptor compared to healthy and mild cognitive impaired groups, while low-affinity p75 type is reduced only in the nucleus basalis of women with AD [288, 289]. The reduction in the number of receptors related to neuronal survival in females depicted in (Fig. 3) is in line with the idea of increased AD susceptibility of this sex. Conversely, the same proportion of the high-affinity trkA receptors in both sexes could counterbalance the greater loss of low-affinity p75 receptors in females, maintaining the neurotrophic signaling.

The apolipoprotein D (ApoD) expression is different during aging in healthy women and men, but not in AD patients, in which ApoD expression is high in both sexes [290]. For example, there is an age-related increase in ApoD expression in cells of several brain areas in healthy women (but not men), with no signs of degeneration or death. Given that ApoD neuroprotective actions induce glial activation [291] and scavenging properties against lipid oxidation products surrounding the amyloid plaque [292], this protein might be involved in AD sex differences in two possible ways. The ApoD increase only in healthy aging women may denote the early need for their neuroprotective actions against pathogenic factors (e.g. Aβ oligomers and fibrils initial production). Alternatively, there might be a delayed ApoD protective response in men, in which ApoD levels would only increase when the AD is already installed (see Fig. 3).

NEP is one of the enzymes responsible for the degradation of Aβ [293]. It is significantly reduced with aging, as previously reported in non-Tg mice [294] and AD Tg models [295, 296]. The NEP decrease in 3xTg-AD mice was more exacerbated

than that found in non-Tg mice and more prominently in females [297]. In addition, ovariectomy significantly reduced the cerebral NEP activity and E2 replacement restored this activity [298], suggesting that the activity is E2-dependent. Hirata-Fukae and coworkers [297] found that 1) when mice did not display plaque formation yet, Aβ levels were not different between the sexes and 2) female plaque-bearing mice showed significantly high Aβ levels related to an enhanced BACE activity and suppressed amount of NEP. These results suggest that both the increased Aβ production and reduced degradation may contribute to the higher risk of AD in female mice (Fig. 3).

Reelin (RL) is a chemotactic glycoprotein from the extracellular matrix that is widely produced during neurodevelopment and participates in neuronal migration [299]. In the adult brain, RL plays a role in the memory and synaptic plasticity by modulation of NMDA receptor activity, enhancement of LTP [300], and stabilization of the cytoskeleton actin [301]. The RL relationship with AD involves AβPP trafficking and processing [302] and the reduction in Aβ levels is possibly related to the enhancement of the non-amyloidogenic cascade [303]. RL pathway also prevents tau hyperphosphorylation [304] and slows the fibrils formation through a direct interaction with soluble $Aβ_{42}$ peptides [305]. Moreover, reduced RL expression accelerates Aβ plaque formation and tau pathology in Tg AD mice [306] and cognitive decline during normal aging of rodents and primates [307]. On the other hand, in 3xTg-AD mice there was an accumulation of RL in amyloid plaques, creating a precursor condition for senile plaque deposition [307]. This finding is in agreement with the association between RL and amyloid plaques in AD double-Tg mice model [308]. Moreover, Botella-López et al. [309] have shown that cortical RL was 40% higher in AD patients compared to controls. A recent review approached these contradictory results. In the AD brain, Aβ impairs RL signaling pathway, hindering its biological activity, which would result in a compensatory increase of the RL expression [310]. Also recently, Palladino and colleagues [311] showed that the decrease of RL levels is more expressive in the hippocampus and cerebral cortex of female Tg mice (5 to 6 times compared to males). However, in spite of a downregulation of RL expression compared to males, Tg females display fewer Aβ plaques, suggesting that additional factors, other than sex and RL levels, influence the amyloidogenic pathway in this mice model [311]. Of note, a variation in the RL gene

Table 3
Markers possibly related to AD sex differences. Neurochemical (oxidative stress) and molecular (receptors and proteins) factors present variations between the sexes during natural aging and the establishment of AD.

Neurochemical and molecular factors	AD-related markers	♀	♂	References
Oxidative stress	Antioxidants	+	−	[279, 280]
	[Cu]	−	+	[278]
	[Zn]	+	−	
	[Co]	+	−	
	[Mn]	+	−	
Receptors	TrkA	−	−	[288]
	p75	−	+	
	AMPA	−	+	
Proteins	ApoD (no AD)	+	−	[290]
	Neprilysin	−	+	[297]
	Reelin	−	+	[311]

The positive and negative signs indicate a greater or lesser amount of the respective marker in each sex.

is associated with increased risk of AD in women [312]. Table 3 summarizes the possible factors involved in the AD sex differences discussed herein.

Autophagy and changes in white matter are also examples of mechanisms that are linked to the risk for AD. Zhou and coworkers [313] suggested a sex-specific difference in the rate of conduction along myelinated fibers and the reduction of volume of the white matter, being the females most affected. Autophagy induction is also affected by sex and data showed that females have lower basal autophagy, which may unleash greater predisposition to AD [314]. There are several other factors correlated with AD pathophysiology that were not mentioned in the present study, such as neuropeptides (e.g., somatostatin [19] and bradykinin [20]) and other hormones (e.g., luteinizing hormone [315]). However, to our knowledge, these issues have not been approached in terms of sex differences yet.

CURRENT CAVEATS AND PERSPECTIVES

The controversial clinical and epidemiological data about AD sex differences should not be interpreted as a simple product of aging or life expectancy. In other words, the literature should not ignore the pronounced sex differences throughout the brain development that are already based on a considerable body of evidence, mainly in animal models. Our attempt here was to bring together conceptual subsidies in a rationale to embrace hypotheses that would try to elucidate discrepancies between the sexes. Our

point of view is in line with the conception posed by Mazure and Swendsen [316] that the AD research needs to consider sex-specific disabilities and vulnerabilities over the years and not only what brings more susceptibility to one sex compared to the other. The future AD research should discuss the sex differences in several levels of causal approaches and its interactions.

Perhaps the main difficulty in the investigation of AD sex differences is to detect the exact moment of the changes related to the disease, which could emerge in one sex and not in the other. Indeed, most human and animal studies use subjects already affected by the disease, often conducting analyses at a specific time point and disregarding the progressive feature of AD. Other drawback often found in AD research is the mismatched chronology of the neurochemical events and the emergence of the behavioral alterations. Thus, further human and animal model research should overcome these drawbacks by investing in follow-up studies of the same subject (instead of simply separating them into age groups), in addition to better refine the limitations.

On the other hand, the increase in the lifespan of people from emerging and developed countries, together with the increased survival after AD diagnosis due to the advances in treatment, make sexual variations related to the aging process more evident (e.g., ApoD-linked sex differences). Likewise, the research with animal models may vary according to the genotype and lifespan of the AD strain used, and therefore it is important to conduct the investigations with aging- and sex-matched controls, so that correlations of behavioral and physiological biomarkers can be more reliable to the human condition (as reviewed by [123]). Thus, the evaluation at various time points during the disease progression seems to be critical. More systematic and comparative investigations would enable the identification of significant changes and contribute to detect new signaling pathways and therapeutic targets.

Indeed, despite the growing incorporation of female in AD studies, mainly in Tg models, there remains a significant lack of comparative studies between the sexes. This scenario continues in part because of the underrepresentation of females in the experimental designs, which could generate an incomplete understanding of the differences in AD studies [317]. For example, there are several biomarkers known to modulate AD pathophysiology that have already been investigated in one sex (usually in males), but have not been considered potential tar-

gets for the study of AD sex differences. Scientific findings on AD sex differences indicate that females, whether human or not, are more susceptible due to some molecular factors (such as ApoE) and present early alterations related to developmental risk (such as E2 loss and higher stress response) compared to males. Awareness of these differences should encourage studies to surpass the historical disadvantage that females have in scientific reports and evaluate both sexes. Moreover, evidences also suggest that direct factors, which confer greater susceptibility, but also indirect factors that might lead to greater vulnerability to one sex are not immutable and depend on the AD course, sex-linked intrinsic factors and comorbidities. Therefore, it is important to investigate AD under the light of a sex role for its pathophysiology. This may help to overcome some gaps in the understanding of the disease and hence benefit patients and future patients of both sexes.

Finally, our review endorses Fisher and coworkers' suggestion [33] that biological mechanisms intrinsic to sex increase the risk of developing AD, especially those involved with changes during the aging process. They also point out that comparisons of mechanisms converging or shared by both sexes should be encouraged. Future studies should not place male versus female, or highlight the advantages and disadvantages of sex in AD, but rather observe in both sexes details that drive disease control pathways more suitable for one sex. Some authors [318, 319] currently advocate the merits and future directions on the research of sex differences in AD. Among the main recommendations, studies should investigate not only factors directly related to the etiology of the disease, but also comorbidities that knowingly affect and interact with these factors. Moreover, the current and next therapeutic approaches for AD need to be continuously examined in light of the sex differences. Indeed, only recently this topic attracted attention [320] and the lack of information regarding the relationship between pharmacodynamic and pharmacokinetic properties of AD therapeutic agents and sex is worrying. Therefore, more efforts should be made to collect and report data on this issue.

ACKNOWLEDGMENTS

REFERENCES

[1] Farlow MR, Evans RM (1998) Pharmacologic treatment of cognition in Alzheimer's dementia. *Neurology* **51**, S36-S44; discussion S65-S67.

[2] Panidis DK, Matalliotakis IM, Rousso DH, Kourtis AI, Koumantakis EE (2001) The role of estrogen replacement therapy in Alzheimer's disease. *Eur J Obstet Gynecol Reprod Biol* **95**, 86-91.

[3] Jorm AF, Korten AE, Henderson AS (1987) The prevalence of dementia: A quantitative integration of the literature. *Acta Psychiatr Scand* **76**, 465-479.

[4] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003) Alzheimer disease in the US population: Prevalence estimates using the 2000 census. *Arch Neurol* **60**, 1119-1122.

[5] Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A (1995) Prevalence of Alzheimer's disease and vascular dementia: Association with education. The Rotterdam study. *BMJ* **310**, 970-973.

[6] Paganini-Hill A (1998) Estrogen replacement therapy–something to smile about. *Compend Contin Educ Dent Suppl*, S4-8.

[7] Paganini-Hill A, Henderson VW (1998) Estrogen in the treatment and prevention of Alzheimer's disease. *Int J Pharm Compd* **2**, 24-29.

[8] Takeda S, Sato N, Niisato K, Takeuchi D, Kurinami H, Shinohara M, Rakugi H, Kano M, Morishita R (2009) Validation of Abeta1-40 administration into mouse cerebroventricles as an animal model for Alzheimer disease. *Brain Res* **1280**, 137-147.

[9] Reitz C, Brayne C, Mayeux R (2011) Epidemiology of Alzheimer disease. *Nat Rev Neurol* **7**, 137-152.

[10] Herrera E, Caramelli P, Nitrini R (1998) Estudo epidemiologico populacional de demencia na cidade de Catanduva, estado de Sao Paulo, Brasil/Population epidemiologic study of dementia in Catanduva city: State of Sao Paulo, Brazil. *Rev Psiquiatr Clín* **25**, 70-73.

[11] Herrera E, Caramelli P, Silveira ASB, Nitrini R (2002) Epidemiologic survey of dementia in a community-dwelling Brazilian population. *Alzheimer Dis Assoc Disord* **16**, 103-108.

[12] Nitrini R, Caramelli P, Herrera E, Bahia VS, Caixeta LF, Radanovic M, Anghinah R, Charchat-Fichman H, Porto CS, Carthery MT, Hartmann APJ, Huang N, Smid J, Lima EP, Takada LT, Takahashi DY (2004) Incidence of dementia in a community-dwelling Brazilian population. *Alzheimer Dis Assoc Disord* **18**, 241-246.

[13] Mendez MF (2012) Early-onset Alzheimer's disease: Nonamnestic subtypes and type 2 AD. *Arch Med Res* **43**, 677-685.

[14] Tanzi RE, Bertram L (2005) Twenty years of the Alzheimer's disease amyloid hypothesis: A genetic perspective. *Cell* **120**, 545-555.

[15] Walsh DM, Selkoe DJ (2007) A beta oligomers - a decade of discovery. *J Neurochem* **101**, 1172-1184.

[16] Mudher A, Lovestone S (2002) Alzheimer's disease-do tauists and baptists finally shake hands? *Trends Neurosci* **25**, 22-26.

[17] Viña J, Lloret A (2010) Why women have more Alzheimer's disease than men: Gender and mitochondrial toxicity of amyloid-beta peptide. *J Alzheimers Dis* **20**(Suppl 2), S527-S533.

[18] Su B, Wang X, Nunomura A, Moreira PI, Lee HG, Perry G, Smith MA, Zhu X (2008) Oxidative stress signaling in Alzheimer's disease. *Curr Alzheimer Res* **5**, 525-532.

[19] Hama E, Saido TC (2005) Etiology of sporadic Alzheimer's disease: Somatostatin, neprilysin, and amyloid beta peptide. *Med Hypotheses* **65**, 498-500.

[20] Prediger RDS, Medeiros R, Pandolfo P, Duarte FS, Passos GF, Pesquero JB, Campos MM, Calixto JB, Takahashi RN (2008) Genetic deletion or antagonism of kinin B(1) and B(2) receptors improves cognitive deficits in a mouse model of Alzheimer's disease. *Neuroscience* **151**, 631-643.

[21] Torrão AS, Café-Mendes CC, Real CC, Hernandes MS, Ferreira AFB, Santos TO, Chaves-Kirsten GP, Mazucanti CHY, Ferro ES, Scavone C, Britto LRG (2012) Different approaches, one target: Understanding cellular mechanisms of Parkinson's and Alzheimer's diseases. *Rev Bras Psiquiatr* **34**(Suppl 2), S194-S205.

[22] Ronquillo JG, Baer MR, Lester WT (2016) Sex-specific patterns and differences in dementia and Alzheimer's disease using informatics approaches. *J Women Aging* **28**, 403-411.

[23] Mölsä PK, Marttila RJ, Rinne UK (1982) Epidemiology of dementia in a Finnish population. *Acta Neurol Scand* **65**, 541-552.

[24] Bachman DL, Wolf PA, Linn R, Knoefel JE, Cobb J, Belanger A, D'Agostino RB, White LR (1992) Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology* **42**, 115-119.

[25] Hagnell O, Ojesjö L, Rorsman B (1992) Incidence of dementia in the Lundby Study. *Neuroepidemiology* **11**(Suppl 1), 61-66.

[26] Letenneur L, Commenges D, Dartigues JF, Barberger-Gateau P (1994) Incidence of dementia and Alzheimer's disease in elderly community residents of south-western France. *Int J Epidemiol* **23**, 1256-1261.

[27] Brayne C, Gill C, Paykel ES, Huppert F, O'Connor DW (1995) Cognitive decline in an elderly population–a two wave study of change. *Psychol Med* **25**, 673-683.

[28] Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B (1997) Very old women at highest risk of dementia and Alzheimer's disease: Incidence data from the Kungsholmen Project, Stockholm. *Neurology* **48**, 132-138.

[29] Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, Lobo A, Martinez-Lage J, Soininen H, Hofman A (2000) Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* **54**, S10-S15.

[30] Andersen K, Launer LJ, Dewey ME, Letenneur L, Ott A, Copeland JR, Dartigues JF, Kragh-Sorensen P, Baldereschi M, Brayne C, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A (1999) Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. EURODEM Incidence Research Group. *Neurology* **53**, 1992-1997.

[31] Jorm AF, Jolley D (1998) The incidence of dementia: A meta-analysis. *Neurology* **51**, 728-733.

[32] Gao S, Hendrie HC, Hall KS, Hui S (1998) The relationships between age, sex, and the incidence of dementia and Alzheimer disease: A meta-analysis. *Arch Gen Psychiatry* **55**, 809-815.

[33] Fisher DW, Bennett DA, Dong H (2018) Sexual dimorphism in predisposition to Alzheimer's disease. *Neurobiol Aging* **70**, 308-324.

[34] Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, White LR, D'Agostino RB (1993) Incidence of dementia and probable Alzheimer's disease in a general population: The Framingham Study. *Neurology* **43**, 515-519.

[35] Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, Cohen A, Kirk A, Pearson D, Pringsheim T, Venegas-Torres A, Jetté N (2016) The prevalence and incidence of dementia due to Alzheimer's disease: A systematic review and meta-analysis. *Can J Neurol Sci* **43**, S51-S82.

[36] Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A (1999) Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. *Neurology* **52**, 78-84.

[37] Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, Breitner JCS, Cache County Memory Study Investigators (2002) Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache County Study. *JAMA* **288**, 2123-2129.

[38] Schäfer S, Wirths O, Multhaup G, Bayer TA (2007) Gender dependent APP processing in a transgenic mouse model of Alzheimer's disease. *J Neural Transm* **114**, 387-394.

[39] May M (2016) Sex on the brain: Unraveling the differences between women and men in neurodegenerative disease. *Nat Med* **22**, 1370-1372.

[40] Van Dam D, De Deyn PP (2011) Animal models in the drug discovery pipeline for Alzheimer's disease. *Br J Pharmacol* **164**, 1285-1300.

[41] Duyckaerts C, Potier M-C, Delatour B (2008) Alzheimer disease models and human neuropathology: Similarities and differences. *Acta Neuropathol (Berl)* **115**, 5-38.

[42] Cummings BJ, Head E, Ruehl W, Milgram NW, Cotman CW (1996) The canine as an animal model of human aging and dementia. *Neurobiol Aging* **17**, 259-268.

[43] Gunn-Moore DA, McVee J, Bradshaw JM, Pearson GR, Head E, Gunn-Moore FJ (2006) Ageing changes in cat brains demonstrated by beta-amyloid and AT8-immunoreactive phosphorylated tau deposits. *J Feline Med Surg* **8**, 234-242.

[44] Kimura N, Tanemura K, Nakamura S, Takashima A, Ono F, Sakakibara I, Ishii Y, Kyuwa S, Yoshikawa Y (2003) Age-related changes of Alzheimer's disease-associated proteins in cynomolgus monkey brains. *Biochem Biophys Res Commun* **310**, 303-311.

[45] Voytko ML, Tinkler GP (2004) Cognitive function and its neural mechanisms in nonhuman primate models of aging, Alzheimer disease, and menopause. *Front Biosci J Virtual Libr* **9**, 1899-1914.

[46] Braak H, Braak E, Strothjohann M (1994) Abnormally phosphorylated tau protein related to the formation of neu-

rofibrillary tangles and neuropil threads in the cerebral cortex of sheep and goat. *Neurosci Lett* **171**, 1-4.

[47] Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* **2**, 1403.

[48] Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR (1981) Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol* **10**, 122-126.

[49] Trabace L, Cassano T, Steardo L, Pietra C, Villetti G, Kendrick KM, Cuomo V (2000) Biochemical and neurobehavioral profile of CHF2819, a novel, orally active acetylcholinesterase inhibitor for Alzheimer's disease. *J Pharmacol Exp Ther* **294**, 187-194.

[50] Ahmed T, Gilani A-H (2009) Inhibitory effect of curcuminoids on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia may explain medicinal use of turmeric in Alzheimer's disease. *Pharmacol Biochem Behav* **91**, 554-559.

[51] Wong KK-K, Ho MT-W, Lin HQ, Lau K-F, Rudd JA, Chung RC-K, Fung K-P, Shaw P-C, Wan DC-C (2010) Cryptotanshinone, an acetylcholinesterase inhibitor from Salvia miltiorrhiza, ameliorates scopolamine-induced amnesia in Morris water maze task. *Planta Med* **76**, 228-234.

[52] Lawlor P, Young D (2010) Aβ infusion and related models of Alzheimer dementia. In *Animal models of Dementia*, De Deyn PP, Van Dam D, eds. Springer Science + Business Media, New York.

[53] Harkany T, O'Mahony S, Kelly JP, Soós K, Törõ I, Penke B, Luiten PG, Nyakas C, Gulya K, Leonard BE (1998) Beta-amyloid(Phe(SO3H)24)25-35 in rat nucleus basalis induces behavioral dysfunctions, impairs learning and memory and disrupts cortical cholinergic innervation. *Behav Brain Res* **90**, 133-145.

[54] Yamada M, Chiba T, Sasabe J, Nawa M, Tajima H, Niikura T, Terashita K, Aiso S, Kita Y, Matsuoka M, Nishimoto I (2005) Implanted cannula-mediated repetitive administration of Abeta25-35 into the mouse cerebral ventricle effectively impairs spatial working memory. *Behav Brain Res* **164**, 139-146.

[55] Sipos E, Kurunczi A, Kasza A, Horváth J, Felszeghy K, Laroche S, Toldi J, Párducz A, Penke B, Penke Z (2007) Beta-amyloid pathology in the entorhinal cortex of rats induces memory deficits: Implications for Alzheimer's disease. *Neuroscience* **147**, 28-36.

[56] Szkudelski T (2001) The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res* **50**, 537-546.

[57] Hoyer S (2002) The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: An update. *J Neural Transm* **109**, 341-360.

[58] Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science* **274**, 99-102.

[59] Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Bürki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M, Sommer B (1997) Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proc Natl Acad Sci U S A* **94**, 13287-13292.

[60] Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eck-man C, Hardy J, Hutton M, McGowan E (2001) Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science* **293**, 1487-1491.

[61] Yoshiyama Y, Higuchi M, Zhang B, Huang S-M, Iwata N, Saido TC, Maeda J, Suhara T, Trojanowski JQ, Lee VM-Y (2007) Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* **53**, 337-351.

[62] Dumont M, Stack C, Elipenahli C, Jainuddin S, Gerges M, Starkova NN, Yang L, Starkov AA, Beal F (2011) Behavioral deficit, oxidative stress, and mitochondrial dysfunction precede tau pathology in P301S transgenic mice. *FASEB J* **25**, 4063-4072.

[63] SantaCruz K (2005) Tau suppression in a neurodegenerative mouse model improves memory function. *Science* **309**, 476-481.

[64] Yue M, Hanna A, Wilson J, Roder H, Janus C (2011) Sex difference in pathology and memory decline in rTg4510 mouse model of tauopathy. *Neurobiol Aging* **32**, 590-603.

[65] Van Dam D, Vloeberghs E, Abramowski D, Staufenbiel M, De Deyn PPP (2005) APP23 mice as a model of Alzheimer's disease: An example of a transgenic approach to modeling a CNS disorder. *CNS Spectr* **10**, 207-222.

[66] Basak J, Holtzman D (2010) APP-based transgenic models of Alzheimer's dementia: The PDAPP Model. In *Animal Models of Dementia*, De Deyn PP, Van Dam D, eds. Springer Science + Business Media, New York.

[67] Deacon R (2010) APP-based transgenic models of Alzheimer dementia: The Tg2576 mouse. In *Animal Models of Dementia*, De Deyn PP, Van Dam D, eds. Springer Science + Business Media, New York.

[68] Hong C-S, Goins WF, Goss JR, Burton EA, Glorioso JC (2006) Herpes simplex virus RNAi and neprilysin gene transfer vectors reduce accumulation of Alzheimer's disease-related amyloid-beta peptide *in vivo*. *Gene Ther* **13**, 1068-1079.

[69] Lawlor PA, Bland RJ, Das P, Price RW, Holloway V, Smithson L, Dicker BL, During MJ, Young D, Golde TE (2007) Novel rat Alzheimer's disease models based on AAV-mediated gene transfer to selectively increase hippocampal Abeta levels. *Mol Neurodegener* **2**, 11.

[70] Do Carmo S, Cuello A (2013) Modeling Alzheimer's disease in transgenic rats. *Mol Neurodegener* **8**, 37.

[71] Mielke MM, Vemuri P, Rocca WA (2014) Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. *Clin Epidemiol* **6**, 37-48.

[72] Teixeira JB, Souza Junior PRB de, Higa J, Theme Filha MM (2015) Mortality from Alzheimer's disease in Brazil, 2000-2009. *Cad Saúde Pública* **31**, 850-860.

[73] Alzheimer's Association (2014) 2014 Alzheimer's disease facts and figures. *Alzheimers Dement* **10**, e47-92.

[74] Shriver M, Alzheimer's Association (2010) *The Shriver Report: A Woman's National Takes on Alzheimer's*, Simon & Schuster, Inc., New York.

[75] Woods NF, Tsui AO (2014) Editorial: Epidemiologic approaches to women's health. *Epidemiol Rev* **36**, 1-4.

[76] Institute of Medicine (US) Committee on Women's Health Research (2010) *Women's Health Research: Progress, Pitfalls, and Promise*, National Academies Press (US), Washington (DC).

[77] Rocca WA, Mielke MM, Vemuri P, Miller VM (2014) Sex and gender differences in the causes of dementia: A narrative review. *Maturitas* **79**, 196-201.

[78] Namba Y, Tomonaga M, Kawasaki H, Otomo E, Ikeda K (1991) Apolipoprotein E immunoreactivity in

cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. *Brain Res* **541**, 163-166.

[79] Uchihara T, Duyckaerts C, He Y, Kobayashi K, Seilhean D, Amouyel P, Hauw JJ (1995) ApoE immunoreactivity and microglial cells in Alzheimer's disease brain. *Neurosci Lett* **195**, 5-8.

[80] Uchihara T, Duyckaerts C, Lazarini F, Mokhtari K, Seilhean D, Amouyel P, Hauw JJ (1996) Inconstant apolipoprotein E (ApoE)-like immunoreactivity in amyloid beta protein deposits: Relationship with APOE genotype in aging brain and Alzheimer's disease. *Acta Neuropathol (Berl)* **92**, 180-185.

[81] Irizarry MC, Cheung BS, Rebeck GW, Paul SM, Bales KR, Hyman BT (2000) Apolipoprotein E affects the amount, form, and anatomical distribution of amyloid beta-peptide deposition in homozygous APP(V717F) transgenic mice. *Acta Neuropathol (Berl)* **100**, 451-458.

[82] Barron AM, Pike CJ (2012) Sex hormones, aging, and Alzheimer's disease. *Front Biosci (Elite Ed)* **4**, 976-997.

[83] Broestl L, Worden K, Wang D, Devidze N, Kim D, Chang K, Yu GQ, Palop JJ, Miller BL, Arnold AP, Mucke L, Dubal DB (2015) The X-chromosome decreases mortality and confers resilience against Alzheimer's deficits: M225WIP. *Ann Neurol* **78**, S87.

[84] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.

[85] Liu C-C, Liu C-C, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nat Rev Neurol* **9**, 106-118.

[86] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* **278**, 1349-1356.

[87] Damoiseaux JS, Seeley WW, Zhou J, Shirer WR, Coppola G, Karydas A, Rosen HJ, Miller BL, Kramer JH, Greicius MD, Alzheimer's Disease Neuroimaging Initiative (2012) Gender modulates the APOE ε4 effect in healthy older adults: Convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci* **32**, 8254-8262.

[88] Deming Y, Dumitrescu L, Barnes LL, Thambisetty M, Kunkle B, Gifford KA, Bush WS, Chibnik LB, Mukherjee S, De Jager PL, Kukull W, Huentelman M, Crane PK, Resnick SM, Keene CD, Montine TJ, Schellenberg GD, Haines JL, Zetterberg H, Blennow K, Larson EB, Johnson SC, Albert M, Moghekar A, del Aguila JL, Fernandez MV, Budde J, Hassenstab J, Fagan AM, Riemenschneider M, Petersen RC, Minthon L, Chao MJ, Van Deerlin VM, Lee VM-Y, Shaw LM, Trojanowski JQ, Peskind ER, Li G, Davis LK, Sealock JM, Cox NJ, Goate AM, Bennett DA, Schneider JA, Jefferson AL, Cruchaga C, Hohman TJ (2018) Sex-specific genetic predictors of Alzheimer's disease biomarkers. *Acta Neuropathol.* doi: 10.1007/s00401-018-1881-4

[89] Sampedro F, Vilaplana E, de Leon MJ, Alcolea D, Pegueroles J, Montal V, Carmona-Iragui M, Sala I, Sánchez-Saudinos M-B, Antón-Aguirre S, Morenas-Rodríguez E, Camacho V, Falcón C, Pavía J, Ros D,

Clarimón J, Blesa R, Lleó A, Fortea J, Alzheimer's Disease Neuroimaging Initiative (2015) APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. *Oncotarget* **6**, 26663-26674.

[90] Fleisher AS, Sun S, Taylor C, Ward CP, Gamst AC, Petersen RC, Jack CR, Aisen PS, Thal LJ (2008) Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. *Neurology* **70**, 191-199.

[91] Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD (1993) Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 9649-9653.

[92] Ohm TG, Kirca M, Bohl J, Scharnagl H, Gross W, März W (1995) Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. *Neuroscience* **66**, 583-587.

[93] Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative Investigators (2014) Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol* **75**, 563-573.

[94] Neu SC, Pa J, Kukull W, Beekly D, Kuzma A, Gangadharan P, Wang L-S, Romero K, Arneric SP, Redolfi A, Orlandi D, Frisoni GB, Au R, Devine S, Auerbach S, Espinosa A, Boada M, Ruiz A, Johnson SC, Koscik R, Wang J-J, Hsu W-C, Chen Y-L, Toga AW (2017) Apolipoprotein E genotype and sex risk factors for Alzheimer disease: A meta-analysis. *JAMA Neurol* **74**, 1178.

[95] Karch CM, Goate AM (2015) Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biol Psychiatry* **77**, 43-51.

[96] Mangialasche F, Kivipelto M, Solomon A, Fratiglioni L (2012) Dementia prevention: Current epidemiological evidence and future perspective. *Alzheimers Res Ther* **4**, 6.

[97] Solomon A, Kivipelto M, Soininen H (2013) Prevention of Alzheimer's disease: Moving backward through the lifespan. *J Alzheimers Dis* **33**(Suppl 1), S465-S469.

[98] Razay G, Vreugdenhil A, Wilcock G (2007) The metabolic syndrome and Alzheimer disease. *Arch Neurol* **64**, 93-96.

[99] Langbaum JBS, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, Alexander GE, Foster NL, Weiner MW, Koeppe RA, Jagust WJ, Reiman EM, Alzheimer's Disease Neuroimaging Initiative (2009) Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Neuroimage* **45**, 1107-1116.

[100] Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S (2011) Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol* **68**, 51-57.

[101] Willette AA, Johnson SC, Birdsill AC, Sager MA, Christian B, Baker LD, Craft S, Oh J, Statz E, Hermann BP, Jonaitis EM, Koscik RL, La Rue A, Asthana S, Bendlin BB (2015) Insulin resistance predicts brain amyloid deposition in late middle-aged adults. *Alzheimers Dement* **11**, 504-510.e1.

[102] Wang H-X, Gustafson DR, Kivipelto M, Pedersen NL, Skoog I, Windblad B, Fratiglioni L (2012) Education halves the risk of dementia due to apolipoprotein ε4 allele: A collaborative study from the Swedish brain power ini-

tiative. *Neurobiol Aging* **33**, 1007.e1-7.

[103] Karp A, Andel R, Parker MG, Wang H-X, Winblad B, Fratiglioni L (2009) Mentally stimulating activities at work during midlife and dementia risk after age 75: Follow-up study from the Kungsholmen Project. *Am J Geriatr Psychiatry* **17**, 227-236.

[104] Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Roberts RO, Lowe VJ, Kantarci K, Senjem ML, Gunter JL, Boeve BF, Petersen RC, Jack CR (2012) Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. *Ann Neurol* **72**, 730-738.

[105] Vemuri P, Lesnick TG, Przybelski SA, Machulda M, Knopman DS, Mielke MM, Roberts RO, Geda YE, Rocca WA, Petersen RC, Jack CR (2014) Association of lifetime intellectual enrichment with cognitive decline in the older population. *JAMA Neurol* **71**, 1017-1024.

[106] Barro RJ, Lee JW (2013) A new data set of educational attainment in the world, 1950–2010. *J Dev Econ* **104**, 184-198.

[107] Ryan C, Siebens J (2012) *Educational attainment in the United States: 2009. Current population reports*, US Department of Commerce, US Census Bureau, Washington, DC.

[108] Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, Gao S, Unverzagt FW, Langa KM, Larson EB, White LR (2011) Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement* **7**, 80-93.

[109] Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL (2014) Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* **82**, 222-229.

[110] Biasibetti R, Almeida Dos Santos JP, Rodrigues L, Wartchow KM, Suardi LZ, Nardin P, Selistre NG, Vázquez D, Gonçalves C-A (2017) Hippocampal changes in STZ-model of Alzheimer's disease are dependent on sex. *Behav Brain Res* **316**, 205-214.

[111] Bao J, Mahaman YAR, Liu R, Wang J-Z, Zhang Z, Zhang B, Wang X (2017) Sex differences in the cognitive and hippocampal effects of streptozotocin in an animal model of sporadic AD. *Front Aging Neurosci* **9**, 347.

[112] Richetin K, Petsophonsakul P, Roybon L, Guiard BP, Rampon C (2017) Differential alteration of hippocampal function and plasticity in females and males of the APPxPS1 mouse model of Alzheimer's disease. *Neurobiol Aging* **57**, 220-231.

[113] Wang J, Tanila H, Puoliväli J, Kadish I, van Groen T (2003) Gender differences in the amount and deposition of amyloidbeta in APPswe and PS1 double transgenic mice. *Neurobiol Dis* **14**, 318-327.

[114] Ordóñez-Gutiérrez L, Antón M, Wandosell F (2015) Peripheral amyloid levels present gender differences associated with aging in AβPP/PS1 mice. *J Alzheimers Dis* **44**, 1063-1068.

[115] Sturchler-Pierrat C, Staufenbiel M (2000) Pathogenic mechanisms of Alzheimer's disease analyzed in the APP23 transgenic mouse model. *Ann N Y Acad Sci* **920**, 134-139.

[116] Bayer TA, Schäfer S, Simons A, Kemmling A, Kamer T, Tepest R, Eckert A, Schüssel K, Eikenberg O, Sturchler-Pierrat C, Abramowski D, Staufenbiel M, Multhaup G (2003) Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Abeta production in APP23 transgenic mice. *Proc Natl Acad Sci U S A* **100**, 14187-

14192.

[117] Callahan MJ, Lipinski WJ, Bian F, Durham RA, Pack A, Walker LC (2001) Augmented senile plaque load in aged female beta-amyloid precursor protein-transgenic mice. *Am J Pathol* **158**, 1173-1177.

[118] Raber J, Wong D, Buttini M, Orth M, Bellosta S, Pitas RE, Mahley RW, Mucke L (1998) Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: Increased susceptibility of females. *Proc Natl Acad Sci U S A* **95**, 10914-10919.

[119] Cacciottolo M, Christensen A, Moser A, Liu J, Pike CJ, Smith C, LaDu MJ, Sullivan PM, Morgan TE, Dolzhenko E, Charidimou A, Wahlund L-O, Wiberg MK, Shams S, Chiang GC-Y, Alzheimer's Disease Neuroimaging Initiative, Finch CE (2016) The APOE4 allele shows opposite sex bias in microbleeds and Alzheimer's disease of humans and mice. *Neurobiol Aging* **37**, 47-57.

[120] Clinton LK, Billings LM, Green KN, Caccamo A, Ngo J, Oddo S, McGaugh JL, LaFerla FM (2007) Age-dependent sexual dimorphism in cognition and stress response in the 3xTg-AD mice. *Neurobiol Dis* **28**, 76-82.

[121] Park I-H, Hwang EM, Hong HS, Boo JH, Oh SS, Lee J, Jung MW, Bang OY, Kim SU, Mook-Jung I (2003) Lovastatin enhances Abeta production and senile plaque deposition in female Tg2576 mice. *Neurobiol Aging* **24**, 637-643.

[122] Dubal DB, Broestl L, Worden K (2012) Sex and gonadal hormones in mouse models of Alzheimer's disease: What is relevant to the human condition? *Biol Sex Differ* **3**, 24.

[123] Rae EA, Brown RE (2015) The problem of genotype and sex differences in life expectancy in transgenic AD mice. *Neurosci Biobehav Rev* **57**, 238-251.

[124] Zhao L, Mao Z, Woody SK, Brinton RD (2016) Sex differences in metabolic aging of the brain: Insights into female susceptibility to Alzheimer's disease. *Neurobiol Aging* **42**, 69-79.

[125] Kottow MH (2003) The vulnerable and the susceptible. *Bioethics* **17**, 460-471.

[126] Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, Marder K, Sano M, Devanand D, Albert SM, Bylsma F, Tsai WY (1997) Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* **277**, 806-812.

[127] Graves BM, Strand M, Lindsay AR (2006) A reassessment of sexual dimorphism in human senescence: Theory, evidence, and causation. *Am J Hum Biol* **18**, 161-168.

[128] Sundermann EE, Biegon A, Rubin LH, Lipton RB, Mowrey W, Landau S, Maki PM, For the Alzheimer's Disease Neuroimaging Initiative (2016) Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology* **86**, 1368-1376.

[129] Sundermann EE, Maki PM, Rubin LH, Lipton RB, Landau S, Biegon A, For the Alzheimer's Disease Neuroimaging Initiative (2016) Female advantage in verbal memory: Evidence of sex-specific cognitive reserve. *Neurology* **87**, 1916-1924.

[130] Sundermann EE, Biegon A, Rubin LH, Lipton RB, Landau S, Maki PM (2017) Does the female advantage in verbal memory contribute to underestimating Alzheimer's disease pathology in women versus men? *J Alzheimers Dis* **56**, 947-957.

[131] Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA (2005) Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* **62**, 685.

[132] Li R, Singh M (2014) Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol* **35**, 385-403.

[133] Podcasy JL, Epperson CN (2016) Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci* **18**, 437-446.

[134] Moschetti K, Cummings PL, Sorvillo F, Kuo T (2012) Burden of Alzheimer's disease-related mortality in the United States, 1999-2008. *J Am Geriatr Soc* **60**, 1509-1514.

[135] Sinforiani E, Citterio A, Zucchella C, Bono G, Corbetta S, Merlo P, Mauri M (2010) Impact of gender differences on the outcome of Alzheimer's disease. *Dement Geriatr Cogn Disord* **30**, 147-154.

[136] Zanetti O, Solerte SB, Cantoni F (2009) Life expectancy in Alzheimer's disease (AD). *Arch Gerontol Geriatr* **49**, 237-243.

[137] Larson EB, Shadlen M-F, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA (2004) Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med* **140**, 501-509.

[138] Ueki A, Shinjo H, Shimode H, Nakajima T, Morita Y (2001) Factors associated with mortality in patients with early-onset Alzheimer's disease: A five-year longitudinal study. *Int J Geriatr Psychiatry* **16**, 810-815.

[139] Barclay LL, Zemcov A, Blass JP, McDowell FH (1985) Factors associated with duration of survival in Alzheimer's disease. *Biol Psychiatry* **20**, 86-93.

[140] Mölsä PK, Marttila RJ, Rinne UK (1995) Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* **91**, 159-164.

[141] Todd S, Barr S, Roberts M, Passmore AP (2013) Survival in dementia and predictors of mortality: A review: Survival and predictors of mortality in dementia. *Int J Geriatr Psychiatry* **28**, 1109-1124.

[142] Koran MEI, Wagener M, Hohman TJ (2017) Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav* **11**, 205-213.

[143] Christiansen C (1993) Prevention and treatment of osteoporosis with hormone replacement therapy. *Int J Fertil Menopausal Stud* **38**(Suppl 1), 45-54.

[144] Stampfer M, Grodstein F (1994) Cardioprotective effect of hormone replacement therapy. Is not due to selection bias. *BMJ* **309**, 808-809.

[145] McEwen BS, Alves SE, Bulloch K, Weiland NG (1997) Ovarian steroids and the brain: Implications for cognition and aging. *Neurology* **48**, S8-S15.

[146] Birge SJ (1997) The role of estrogen in the treatment of Alzheimer's disease. *Neurology* **48**, S36-S41.

[147] Palacios S, Cifuentes I, Menendez C, von Helde S (2000) The central nervous system and HRT. *Int J Fertil Womens Med* **45**, 13-21.

[148] Galea LAM, Wainwright SR, Roes MM, Duarte-Guterman P, Chow C, Hamson DK (2013) Sex, hormones and neurogenesis in the hippocampus: Hormonal modulation of neurogenesis and potential functional implications. *J Neuroendocrinol* **25**, 1039-1061.

[149] Cooke BM, Woolley CS (2005) Gonadal hormone modulation of dendrites in the mammalian CNS. *J Neurobiol* **64**, 34-46.

[150] Brinton RD (2009) Estrogen-induced plasticity from cells to circuits: Predictions for cognitive function. *Trends Pharmacol Sci* **30**, 212-222.

[151] Gibbs RB (2010) Estrogen therapy and cognition: A review of the cholinergic hypothesis. *Endocr Rev* **31**, 224-253.

[152] Simpkins JW, Yi KD, Yang S-H, Dykens JA (2010) Mitochondrial mechanisms of estrogen neuroprotection. *Biochim Biophys Acta* **1800**, 1113-1120.

[153] De la Fuente M, Baeza I, Guayerbas N, Puerto M, Castillo C, Salazar V, Ariznavarreta C, F-Tresguerres JA (2004) Changes with ageing in several leukocyte functions of male and female rats. *Biogerontology* **5**, 389-400.

[154] Keller ET, Zhang J, Yao Z, Qi Y (2001) The impact of chronic estrogen deprivation on immunologic parameters in the ovariectomized rhesus monkey (Macaca mulatta) model of menopause. *J Reprod Immunol* **50**, 41-55.

[155] Borras C, Gambini J, Vina J (2007) Mitochondrial oxidant generation is involved in determining why females live longer than males. *Front Biosci J Virtual Libr* **12**, 1008-1013.

[156] de la Fuente M, Hernanz A, Guayerbas N, Alvarez P, Alvarado C (2004) Changes with age in peritoneal macrophage functions. Implication of leukocytes in the oxidative stress of senescence. *Cell Mol Biol (Noisy-le-grand)* **50 Online Pub**, OL683-OL690.

[157] De la Fuente M, Hernanz A, Vallejo MC (2005) The immune system in the oxidative stress conditions of aging and hypertension: Favorable effects of antioxidants and physical exercise. *Antioxid Redox Signal* **7**, 1356-1366.

[158] Guayerbas N, Puerto M, Alvarez P, de la Fuente M (2004) Improvement of the macrophage functions in prematurely ageing mice by a diet supplemented with thiolic antioxidants. *Cell Mol Biol (Noisy-le-grand)* **50 Online Pub**, OL677-OL681.

[159] Paganini-Hill A, Henderson VW (1994) Estrogen deficiency and risk of Alzheimer's disease in women. *Am J Epidemiol* **140**, 256-261.

[160] Diaz Brinton R, Chen S, Montoya M, Hsieh D, Minaya J, Kim J, Chu HP (2000) The women's health initiative estrogen replacement therapy is neurotrophic and neuroprotective. *Neurobiol Aging* **21**, 475-496.

[161] Monk D, Brodaty H (2000) Use of estrogens for the prevention and treatment of Alzheimer's disease. *Dement Geriatr Cogn Disord* **11**, 1-10.

[162] Singh M, Sétáló G, Guan X, Warren M, Toran-Allerand CD (1999) Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: Convergence of estrogen and neurotrophin signaling pathways. *J Neurosci* **19**, 1179-1188.

[163] Pike CJ (1999) Estrogen modulates neuronal Bcl-xL expression and beta-amyloid-induced apoptosis: Relevance to Alzheimer's disease. *J Neurochem* **72**, 1552-1563.

[164] Zhang Q-G, Wang R, Khan M, Mahesh V, Brann DW (2008) Role of Dickkopf-1, an antagonist of the Wnt/beta-catenin signaling pathway, in estrogen-induced neuroprotection and attenuation of tau phosphorylation. *J Neurosci* **28**, 8430-8441.

[165] Zheng H, Xu H, Uljon SN, Gross R, Hardy K, Gaynor J, Lafrancois J, Simpkins J, Refolo LM, Petanceska S, Wang R, Duff K (2002) Modulation of A(beta) peptides by estrogen in mouse models. *J Neurochem* **80**, 191-196.

[166] Levin-Allerhand JA, Smith JD (2002) Ovariectomy of young mutant amyloid precursor protein transgenic mice leads to increased mortality. *J Mol Neurosci* **19**, 163-166.

[167] Levin-Allerhand JA, Lominska CE, Wang J, Smith JD (2002) 17Alpha-estradiol and 17beta-estradiol treatments are effective in lowering cerebral amyloid-beta levels in AbetaPPSWE transgenic mice. *J Alzheimers Dis* **4**, 449-

457.

[168] Waring SC, Rocca WA, Petersen RC, O'Brien PC, Tangalos EG, Kokmen E (1999) Postmenopausal estrogen replacement therapy and risk of AD: A population-based study. *Neurology* **52**, 965-970.

[169] Slooter AJ, Bronzova J, Witteman JC, Van Broeckhoven C, Hofman A, van Duijn CM (1999) Estrogen use and early onset Alzheimer's disease: A population-based study. *J Neurol Neurosurg Psychiatry* **67**, 779-781.

[170] Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, Bacal C, Lingle DD, Metter E (1997) A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: The Baltimore Longitudinal Study of Aging. *Neurology* **48**, 1517-1521.

[171] Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R (1996) Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* **348**, 429-432.

[172] Honjo H, Ogino Y, Naitoh K, Urabe M, Kitawaki J, Yasuda J, Yamamoto T, Ishihara S, Okada H, Yonezawa T (1989) In vivo effects by estrone sulfate on the central nervous system-senile dementia (Alzheimer's type). *J Steroid Biochem* **34**, 521-525.

[173] Henderson VW, Paganini-Hill A, Miller BL, Elble RJ, Reyes PF, Shoupe D, McCleary CA, Klein RA, Hake AM, Farlow MR (2000) Estrogen for Alzheimer's disease in women: Randomized, double-blind, placebo-controlled trial. *Neurology* **54**, 295-301.

[174] Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Gamst A, Grundman M, Thomas R, Thal LJ (2000) Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: A randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA* **283**, 1007-1015.

[175] Wang PN, Liao SQ, Liu RS, Liu CY, Chao HT, Lu SR, Yu HY, Wang SJ, Liu HC (2000) Effects of estrogen on cognition, mood, and cerebral blood flow in AD: A controlled study. *Neurology* **54**, 2061-2066.

[176] Cholerton B, Gleason CE, Baker LD, Asthana S (2002) Estrogen and Alzheimer's disease: The story so far. *Drugs Aging* **19**, 405-427.

[177] Fillit HM (2002) The role of hormone replacement therapy in the prevention of Alzheimer disease. *Arch Intern Med* **162**, 1934-1942.

[178] Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J, WHIMS Investigators (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *JAMA* **289**, 2651-2662.

[179] Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH, Women's Health Initiative Memory Study (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* **291**, 2947-2958.

[180] Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, Ockene J, Davatzikos C (2009) Postmenopausal hormone therapy and regional brain volumes: The WHIMS-MRI Study. *Neurology* **72**, 135-142.

[181] Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E (2015) Perimenopause as a neurological transition state. *Nat Rev Endocrinol* **11**, 393-405.

[182] Maki PM (2013) Critical window hypothesis of hormone therapy and cognition: A scientific update on clinical studies. *Menopause* **20**, 695-709.

[183] Rocca WA, Grossardt BR, Shuster LT (2010) Oophorectomy, menopause, estrogen, and cognitive aging: The timing hypothesis. *Neurodegener Dis* **7**, 163-166.

[184] Daniel JM, Bohacek J (2010) The critical period hypothesis of estrogen effects on cognition: Insights from basic research. *Biochim Biophys Acta* **1800**, 1068-1076.

[185] Sherwin BB (2007) The critical period hypothesis: Can it explain discrepancies in the oestrogen-cognition literature? *J Neuroendocrinol* **19**, 77-81.

[186] de Macêdo Medeiros A, Izídio GS, Sousa DS, Macedo PT, Silva AF, Shiramizu VKM, Cabral A, Ribeiro AM, Silva RH (2014) Estrogen levels modify scopolamine-induced amnesia in gonadally intact rats. *Prog Neuropsychopharmacol Biol Psychiatry* **53**, 99-108.

[187] Cornil CA, Ball GF, Balthazart J (2006) Functional significance of the rapid regulation of brain estrogen action: Where do the estrogens come from? *Brain Res* **1126**, 2-26.

[188] Pike CJ (2017) Sex and the development of Alzheimer's disease. *J Neurosci Res* **95**, 671-680.

[189] Carroll JC, Rosario ER, Kreimer S, Villamagna A, Gentzschein E, Stanczyk FZ, Pike CJ (2010) Sex differences in β-amyloid accumulation in 3xTg-AD mice: Role of neonatal sex steroid hormone exposure. *Brain Res* **1366**, 233-245.

[190] Carroll JC, Rosario ER, Villamagna A, Pike CJ (2010) Continuous and cyclic progesterone differentially interact with estradiol in the regulation of Alzheimer-like pathology in female 3xTransgenic-Alzheimer's disease mice. *Endocrinology* **151**, 2713-2722.

[191] Jayaraman A, Carroll JC, Morgan TE, Lin S, Zhao L, Arimoto JM, Murphy MP, Beckett TL, Finch CE, Brinton RD, Pike CJ (2012) 17β-estradiol and progesterone regulate expression of β-amyloid clearance factors in primary neuron cultures and female rat brain. *Endocrinology* **153**, 5467-5479.

[192] Jung JI, Ladd TB, Kukar T, Price AR, Moore BD, Koo EH, Golde TE, Felsenstein KM (2013) Steroids as γ-secretase modulators. *FASEB J* **27**, 3775-3785.

[193] Dang TNT, Dobson-Stone C, Glaros EN, Kim WS, Hallupp M, Bartley L, Piguet O, Hodges JR, Halliday GM, Double KL, Schofield PR, Crouch PJ, Kwok JBJ (2013) Endogenous progesterone levels and frontotemporal dementia: Modulation of TDP-43 and Tau levels *in vitro* and treatment of the A315T TARDBP mouse model. *Dis Model Mech* **6**, 1198-1204.

[194] Amtul Z, Wang L, Westaway D, Rozmahel RF (2010) Neuroprotective mechanism conferred by 17beta-estradiol on the biochemical basis of Alzheimer's disease. *Neuroscience* **169**, 781-786.

[195] Zhao L, Morgan TE, Mao Z, Lin S, Cadenas E, Finch CE, Pike CJ, Mack WJ, Brinton RD (2012) Continuous versus cyclic progesterone exposure differentially regulates hippocampal gene expression and functional profiles. *PloS One* **7**, e31267.

[196] Frye CA, Walf AA (2008) Effects of progesterone administration and APPswe+PSEN1Deltae9 mutation for cognitive performance of mid-aged mice. *Neurobiol Learn Mem* **89**, 17-26.

[197] Nilsen J, Brinton RD (2003) Divergent impact of progesterone and medroxyprogesterone acetate (Provera) on

nuclear mitogen-activated protein kinase signaling. *Proc Natl Acad Sci U S A* **100**, 10506-10511.

[198] Goodman Y, Bruce AJ, Cheng B, Mattson MP (1996) Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid beta-peptide toxicity in hippocampal neurons. *J Neurochem* **66**, 1836-1844.

[199] Hogervorst E, Williams J, Budge M, Barnetson L, Combrinck M, Smith AD (2001) Serum total testosterone is lower in men with Alzheimer's disease. *Neuro Endocrinol Lett* **22**, 163-168.

[200] Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM (2004) Free testosterone and risk for Alzheimer disease in older men. *Neurology* **62**, 188-193.

[201] Rosario ER, Chang L, Stanczyk FZ, Pike CJ (2004) Age-related testosterone depletion and the development of Alzheimer disease. *JAMA* **292**, 1431-1432.

[202] Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ (2011) Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol Aging* **32**, 604-613.

[203] Verdile G, Laws SM, Henley D, Ames D, Bush AI, Ellis KA, Faux NG, Gupta VB, Li Q-X, Masters CL, Pike KE, Rowe CC, Szoeke C, Taddei K, Villemagne VL, Martins RN, AIBL Research Group (2014) Associations between gonadotropins, testosterone and β amyloid in men at risk of Alzheimer's disease. *Mol Psychiatry* **19**, 69-75.

[204] Tan RS (2013) Testosterone effect on brain metabolism in elderly patients with Alzheimer's disease: Comparing two cases at different disease stages. *Aging Clin Exp Res* **25**, 343-347.

[205] Tan RS, Pu SJ (2003) A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male* **6**, 13-17.

[206] Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Bremner W, Peskind ER, Raskind MA, Craft S (2005) Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* **64**, 2063-2068.

[207] Rosario ER, Chang L, Beckett TL, Carroll JC, Paul Murphy M, Stanczyk FZ, Pike CJ (2009) Age-related changes in serum and brain levels of androgens in male Brown Norway rats. *Neuroreport* **20**, 1534-1537.

[208] Rosario ER, Carroll JC, Pike CJ (2012) Evaluation of the effects of testosterone and luteinizing hormone on regulation of ββ-amyloid in male 3xTg-AD mice. *Brain Res* **1466**, 137-145.

[209] McAllister C, Long J, Bowers A, Walker A, Cao P, Honda S-I, Harada N, Staufenbiel M, Shen Y, Li R (2010) Genetic targeting aromatase in male amyloid precursor protein transgenic mice down-regulates beta-secretase (BACE1) and prevents Alzheimer-like pathology and cognitive impairment. *J Neurosci* **30**, 7326-7334.

[210] Pike CJ (2001) Testosterone attenuates beta-amyloid toxicity in cultured hippocampal neurons. *Brain Res* **919**, 160-165.

[211] Zhang Y, Champagne N, Beitel LK, Goodyer CG, Trifiro M, LeBlanc A (2004) Estrogen and androgen protection of human neurons against intracellular amyloid beta1-42 toxicity through heat shock protein 70. *J Neurosci* **24**, 5315-5321.

[212] Gouras GK, Xu H, Gross RS, Greenfield JP, Hai B, Wang R, Greengard P (2000) Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. *Proc Natl Acad Sci U S A* **97**, 1202-1205.

[213] Ahlbom E, Prins GS, Ceccatelli S (2001) Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. *Brain Res* **892**, 255-262.

[214] Papasozomenos SC, Shanavas A (2002) Testosterone prevents the heat shock-induced overactivation of glycogen synthase kinase-3 beta but not of cyclin-dependent kinase 5 and c-Jun NH2-terminal kinase and concomitantly abolishes hyperphosphorylation of tau: Implications for Alzheimer's disease. *Proc Natl Acad Sci U S A* **99**, 1140-1145.

[215] Hammond J, Le Q, Goodyer C, Gelfand M, Trifiro M, LeBlanc A (2001) Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. *J Neurochem* **77**, 1319-1326.

[216] Sapolsky R (1996) Stress, glucocorticoids, and damage to the nervous system: The current state of confusion. *Stress* **1**, 1-19.

[217] Gould E, Tanapat P, McEwen BS, Flügge G, Fuchs E (1998) Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc Natl Acad Sci U S A* **95**, 3168-3171.

[218] Gourley SL, Swanson AM, Koleske AJ (2013) Corticosteroid-induced neural remodeling predicts behavioral vulnerability and resilience. *J Neurosci* **33**, 3107-3112.

[219] Tadavarty R, Kaan TKY, Sastry BR (2009) Long-term depression of excitatory synaptic transmission in rat hippocampal CA1 neurons following sleep-deprivation. *Exp Neurol* **216**, 239-242.

[220] Kamal A, Ramakers GMJ, Altinbilek B, Kas MJH (2014) Social isolation stress reduces hippocampal long-term potentiation: Effect of animal strain and involvement of glucocorticoid receptors. *Neuroscience* **256**, 262-270.

[221] Rothman SM, Mattson MP (2010) Adverse stress, hippocampal networks, and Alzheimer's disease. *Neuromolecular Med* **12**, 56-70.

[222] Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ (1998) Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* **1**, 69-73.

[223] Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, McEwen BS, Morrison JH (2004) Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience* **125**, 1-6.

[224] Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS (2006) Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci* **26**, 7870-7874.

[225] Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E (1997) Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J Neurosci* **17**, 2492-2498.

[226] Simon M, Czéh B, Fuchs E (2005) Age-dependent susceptibility of adult hippocampal cell proliferation to chronic psychosocial stress. *Brain Res* **1049**, 244-248.

[227] Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, Tu MT (2005) Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology* **30**, 225-242.

[228] Plessow F, Kiesel A, Kirschbaum C (2012) The stressed prefrontal cortex and goal-directed behaviour: Acute psychosocial stress impairs the flexible implementation of task goals. *Exp Brain Res* **216**, 397-408.

[229] Dong H, Csernansky JG (2009) Effects of stress and stress hormones on amyloid-beta protein and plaque deposition. *J Alzheimers Dis* **18**, 459-469.

[230] Hoogendijk WJG, Meynen G, Endert E, Hofman MA, Swaab DF (2006) Increased cerebrospinal fluid cortisol level in Alzheimer's disease is not related to depression. *Neurobiol Aging* **27**, 780.e1-780.e2.

[231] Mejía S, Giraldo M, Pineda D, Ardila A, Lopera F (2003) Nongenetic factors as modifiers of the age of onset of familial Alzheimer's disease. *Int Psychogeriatr* **15**, 337-349.

[232] Davis KL, Davis BM, Greenwald BS, Mohs RC, Mathé AA, Johns CA, Horvath TB (1986) Cortisol and Alzheimer's disease, I: Basal studies. *Am J Psychiatry* **143**, 300-305.

[233] Hatzinger M, Z'Brun A, Hemmeter U, Seifritz E, Baumann F, Holsboer-Trachsler E, Heuser IJ (1995) Hypothalamic-pituitary-adrenal system function in patients with Alzheimer's disease. *Neurobiol Aging* **16**, 205-209.

[234] Peskind ER, Raskind MA, Wingerson D, Pascualy M, Thal LJ, Dobie DJ, Wilkinson CW (1996) Hypothalamic-pituitary-adrenocortical axis responses to physostigmine: Effects of Alzheimer's disease and gender. *Biol Psychiatry* **40**, 61-68.

[235] Carlson LE, Sherwin BB, Chertkow HM (1999) Relationships between dehydroepiandrosterone sulfate (DHEAS) and cortisol (CRT) plasma levels and everyday memory in Alzheimer's disease patients compared to healthy controls. *Horm Behav* **35**, 254-263.

[236] Deshmukh VD, Deshmukh SV (1990) Stress-adaptation failure hypothesis of Alzheimer's disease. *Med Hypotheses* **32**, 293-295.

[237] Rosenblitt JC, Soler H, Johnson SE, Quadagno DM (2001) Sensation seeking in men and women: Exploring the link. *Horm Behav* **40**, 396-402.

[238] Kraemer S (2000) The fragile male. *BMJ* **321**, 1609-1612.

[239] Owens IPF (2002) Ecology and evolution. Sex differences in mortality rate. *Science* **297**, 2008-2009.

[240] Mazur A (1995) Biosocial models of deviant behavior among male army veterans. *Biol Psychol* **41**, 271-293.

[241] Stefanski V, Grüner S (2006) Gender difference in basal and stress levels of peripheral blood leukocytes in laboratory rats. *Brain Behav Immun* **20**, 369-377.

[242] Zietz B, Hrach S, Schölmerich J, Straub RH (2001) Differential age-related changes of hypothalamus - pituitary - adrenal axis hormones in healthy women and men - role of interleukin 6. *Exp Clin Endocrinol Diabetes* **109**, 93-101.

[243] Giménez-Llort L, Arranz L, Maté I, De la Fuente M (2008) Gender-specific neuroimmunoendocrine aging in a triple-transgenic 3xTg-AD mouse model for Alzheimer's disease and its relation with longevity. *Neuroimmunomodulation* **15**, 331-343.

[244] Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC (2005) A meta-analysis of cortisol response to challenge in human aging: Importance of gender. *Psychoneuroendocrinology* **30**, 80-91.

[245] Wolf OT, Schommer NC, Hellhammer DH, McEwen BS, Kirschbaum C (2001) The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology* **26**, 711-720.

[246] Almela M, Hidalgo V, Villada C, van der Meij L, Espín L, Gómez-Amor J, Salvador A (2011) Salivary alpha-amylase response to acute psychosocial stress: The impact of age. *Biol Psychol* **87**, 421-429.

[247] Fukumoto N, Fujii T, Combarros O, Kamboh MI, Tsai S-J, Matsushita S, Nacmias B, Comings DE, Arboleda H, Ingelsson M, Hyman BT, Akatsu H, Grupe A, Nishimura AL, Zatz M, Mattila KM, Rinne J, Goto Y, Asada T, Nakamura S, Kunugi H (2010) Sexually dimorphic effect of the Val66Met polymorphism of BDNF on susceptibility to Alzheimer's disease: New data and meta-analysis. *Am J Med Genet B Neuropsychiatr Genet* **153B**, 235-242.

[248] Shalev I, Lerer E, Israel S, Uzefovsky F, Gritsenko I, Mankuta D, Ebstein RP, Kaitz M (2009) BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. *Psychoneuroendocrinology* **34**, 382-388.

[249] Li G-D, Bi R, Zhang D-F, Xu M, Luo R, Wang D, Fang Y, Li T, Zhang C, Yao Y-G (2017) Female-specific effect of the BDNF gene on Alzheimer's disease. *Neurobiol Aging* **53**, 192.e11-192.e19.

[250] Yamaura K, Bi Y, Ishiwatari M, Oishi N, Fukata H, Ueno K (2013) Sex differences in stress reactivity of hippocampal BDNF in mice are associated with the female preponderance of decreased locomotor activity in response to restraint stress. *Zoolog Sci* **30**, 1019-1024.

[251] Martisova E, Aisa B, Guereñu G, Ramírez MJ (2013) Effects of early maternal separation on biobehavioral and neuropathological markers of Alzheimer's disease in adult male rats. *Curr Alzheimer Res* **10**, 420-432.

[252] Yang C, Guo X, Wang GH, Wang HL, Liu ZC, Liu H, Zhu ZX, Li Y (2014) Changes in tau phosphorylation levels in the hippocampus and frontal cortex following chronic stress. *Braz J Med Biol Res* **47**, 237-244.

[253] Cuadrado-Tejedor M, Ricobaraza A, Frechilla D, Franco R, Pérez-Mediavilla A, Garcia-Osta A (2012) Chronic mild stress accelerates the onset and progression of the Alzheimer's disease phenotype in Tg2576 mice. *J Alzheimers Dis* **28**, 567-578.

[254] Briones A, Gagno S, Martisova E, Dobarro M, Aisa B, Solas M, Tordera R, Ramírez M (2012) Stress-induced anhedonia is associated with an increase in Alzheimer's disease-related markers. *Br J Pharmacol* **165**, 897-907.

[255] Yan Y, Dominguez S, Fisher DW, Dong H (2018) Sex differences in chronic stress responses and Alzheimer's disease. *Neurobiol Stress* **8**, 120-126.

[256] Bangasser DA, Dong H, Carroll J, Plona Z, Ding H, Rodriguez L, McKennan C, Csernansky JG, Seeholzer SH, Valentino RJ (2017) Corticotropin-releasing factor overexpression gives rise to sex differences in Alzheimer's disease-related signaling. *Mol Psychiatry* **22**, 1126-1133.

[257] Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM (2006) Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci* **26**, 9047-9056.

[258] Touma C, Ambrée O, Görtz N, Keyvani K, Lewejohann L, Palme R, Paulus W, Schwarze-Eicker K, Sachser N (2004) Age- and sex-dependent development of adrenocortical hyperactivity in a transgenic mouse model of Alzheimer's disease. *Neurobiol Aging* **25**, 893-904.

[259] Hartmann A, Veldhuis JD, Deuschle M, Standhardt H, Heuser I (1997) Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: Ultradian secretory pulsatility and diurnal variation. *Neurobiol Aging* **18**, 285-289.

[260] Woiciechowsky C, Schöning B, Lanksch WR, Volk HD, Döcke WD (1999) Mechanisms of brain-mediated systemic anti-inflammatory syndrome causing immunodepression. *J Mol Med Berl Ger* **77**, 769-780.

[261] Aspinall R (2000) Longevity and the immune response. *Biogerontology* **1**, 273-278.

[262] Weinstein Y, Ran S, Segal S (1984) Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse. *J Immunol* **132**, 656-661.

[263] Caruso C, Candore G, Romano GC, Lio D, Bonafè M, Valensin S, Franceschi C (2001) Immunogenetics of longevity. Is major histocompatibility complex polymorphism relevant to the control of human longevity? A review of literature data. *Mech Ageing Dev* **122**, 445-462.

[264] Caruso C, Accardi G, Virruso C, Candore G (2013) Sex, gender and immunosenescence: A key to understand the different lifespan between men and women? *Immun Ageing* **10**, 20.

[265] Lapane KL, Gambassi G, Landi F, Sgadari A, Mor V, Bernabei R (2001) Gender differences in predictors of mortality in nursing home residents with AD. *Neurology* **56**, 650-654.

[266] Bush AI, Pettingell WH, Multhaup G, d Paradis M, Vonsattel JP, Gusella JF, Beyreuther K, Masters CL, Tanzi RE (1994) Rapid induction of Alzheimer A beta amyloid formation by zinc. *Science* **265**, 1464-1467.

[267] Atwood CS, Scarpa RC, Huang X, Moir RD, Jones WD, Fairlie DP, Tanzi RE, Bush AI (2000) Characterization of copper interactions with alzheimer amyloid beta peptides: Identification of an attomolar-affinity copper binding site on amyloid beta1-42. *J Neurochem* **75**, 1219-1233.

[268] Huang X, Atwood CS, Hartshorn MA, Multhaup G, Goldstein LE, Scarpa RC, Cuajungco MP, Gray DN, Lim J, Moir RD, Tanzi RE, Bush AI (1999) The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry* **38**, 7609-7616.

[269] Perry G, Cash AD, Smith MA (2002) Alzheimer disease and oxidative stress. *J Biomed Biotechnol* **2**, 120-123.

[270] Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G (2000) Oxidative stress in Alzheimer's disease. *Biochim Biophys Acta* **1502**, 139-144.

[271] Loeffler DA, LeWitt PA, Juneau PL, Sima AA, Nguyen HU, DeMaggio AJ, Brickman CM, Brewer GJ, Dick RD, Troyer MD, Kanaley L (1996) Increased regional brain concentrations of ceruloplasmin in neurodegenerative disorders. *Brain Res* **738**, 265-274.

[272] Deibel MA, Ehmann WD, Markesbery WR (1996) Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: Possible relation to oxidative stress. *J Neurol Sci* **143**, 137-142.

[273] Plantin LO, Lying-Tunell U, Kristensson K (1987) Trace elements in the human central nervous system studied with neutron activation analysis. *Biol Trace Elem Res* **13**, 69-75.

[274] Rao K, Rao R, Shanmugavelu P, Menon R (1999) Trace elements in Alzheimer's disease brain: A new hypothesis. *Alzheimers Rep* **2**, 241-246.

[275] Maynard CJ, Cappai R, Volitakis I, Cherny RA, White AR, Beyreuther K, Masters CL, Bush AI, Li Q-X (2002) Overexpression of Alzheimer's disease amyloid-beta opposes the age-dependent elevations of brain copper and iron. *J Biol Chem* **277**, 44670-44676.

[276] Phinney AL, Drisaldi B, Schmidt SD, Lugowski S, Coronado V, Liang Y, Horne P, Yang J, Sekoulidis J, Coomaraswamy J, Chishti MA, Cox DW, Mathews PM, Nixon RA, Carlson GA, St George-Hyslop P, Westaway D (2003) *In vivo* reduction of amyloid-beta by a mutant copper transporter. *Proc Natl Acad Sci U S A* **100**, 14193-14198.

[277] Schuessel K, Leutner S, Cairns NJ, Müller WE, Eckert A (2004) Impact of gender on upregulation of antioxidant defence mechanisms in Alzheimer's disease brain. *J Neural Transm* **111**, 1167-1182.

[278] Maynard CJ, Cappai R, Volitakis I, Cherny RA, Masters CL, Li Q-X, Bush AI (2006) Gender and genetic background effects on brain metal levels in APP transgenic and normal mice: Implications for Alzheimer beta-amyloid pathology. *J Inorg Biochem* **100**, 952-962.

[279] Liu H, Harrell LE, Shenvi S, Hagen T, Liu R-M (2005) Gender differences in glutathione metabolism in Alzheimer's disease. *J Neurosci Res* **79**, 861-867.

[280] Viveros M-P, Arranz L, Hernanz A, Miquel J, De la Fuente M (2007) A model of premature aging in mice based on altered stress-related behavioral response and immunosenescence. *Neuroimmunomodulation* **14**, 157-162.

[281] Haywood S (1979) The effect of the sex of weaned rats on the accumulation of dietary copper in their livers. *J Comp Pathol* **89**, 481-487.

[282] Linder MC, Houle PA, Isaacs E, Moor JR, Scott LE (1979) Copper regulation of ceruloplasmin in copper-deficient rats. *Enzyme* **24**, 23-35.

[283] Bremner I, Williams RB, Young BW (1981) The effects of age, sex, and zinc status on the accumulation of (copper, zinc)- metallothionein in rat kidneys. *J Inorg Biochem* **14**, 135-146.

[284] Nederbragt H (1985) Strain- and sex-dependent differences in response to a single high dose of copper in the rat. *Comp Biochem Physiol C* **81**, 425-431.

[285] Bush AI, Tanzi RE (2002) The galvanization of beta-amyloid in Alzheimer's disease. *Proc Natl Acad Sci U S A* **99**, 7317-7319.

[286] Lee J-Y, Cole TB, Palmiter RD, Suh SW, Koh J-Y (2002) Contribution by synaptic zinc to the gender-disparate plaque formation in human Swedish mutant APP transgenic mice. *Proc Natl Acad Sci U S A* **99**, 7705-7710.

[287] Lee J-Y, Kim J-H, Hong SH, Lee JY, Cherny RA, Bush AI, Palmiter RD, Koh J-Y (2004) Estrogen decreases zinc transporter 3 expression and synaptic vesicle zinc levels in mouse brain. *J Biol Chem* **279**, 8602-8607.

[288] Counts SE, Che S, Ginsberg SD, Mufson EJ (2011) Gender differences in neurotrophin and glutamate receptor expression in cholinergic nucleus basalis neurons during the progression of Alzheimer's disease. *J Chem Neuroanat* **42**, 111-117.

[289] Salehi A, Ocampo M, Verhaagen J, Swaab DF (2000) P75 neurotrophin receptor in the nucleus basalis of meynert in relation to age, sex, and Alzheimer's disease. *Exp Neurol* **161**, 245-258.

[290] Ordóñez C, Navarro A, Pérez C, Martínez E, del Valle E, Tolivia J (2012) Gender differences in apolipoprotein D expression during aging and in Alzheimer disease. *Neurobiol Aging* **33**, 433.e11-20.

[291] Muffat J, Walker DW (2010) Apolipoprotein D: An overview of its role in aging and age-related diseases. *Cell Cycle* **9**, 269-273.

[292] Li H, Ruberu K, Muñoz SS, Jenner AM, Spiro A, Zhao H, Rassart E, Sanchez D, Ganfornina MD, Karl T, Garner B (2015) Apolipoprotein D modulates amyloid pathology in APP/PS1 Alzheimer's disease mice. *Neurobiol Aging* **36**, 1820-1833.

[293] Iwata N, Higuchi M, Saido TC (2005) Metabolism of amyloid-beta peptide and Alzheimer's disease. *Pharmacol Ther* **108**, 129-148.

[294] Iwata N, Takaki Y, Fukami S, Tsubuki S, Saido TC (2002) Region-specific reduction of A beta-degrading endopeptidase, neprilysin, in mouse hippocampus upon aging. *J Neurosci Res* **70**, 493-500.

[295] Caccamo A, Oddo S, Sugarman MC, Akbari Y, LaFerla FM (2005) Age- and region-dependent alterations in Abeta-degrading enzymes: Implications for Abeta-induced disorders. *Neurobiol Aging* **26**, 645-654.

[296] Lazarov O, Robinson J, Tang Y-P, Hairston IS, Korade-Mirnics Z, Lee VM-Y, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS (2005) Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* **120**, 701-713.

[297] Hirata-Fukae C, Li H-F, Hoe H-S, Gray AJ, Minami SS, Hamada K, Niikura T, Hua F, Tsukagoshi-Nagai H, Horikoshi-Sakuraba Y, Mughal M, Rebeck GW, LaFerla FM, Mattson MP, Iwata N, Saido TC, Klein WL, Duff KE, Aisen PS, Matsuoka Y (2008) Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model. *Brain Res* **1216**, 92-103.

[298] Huang J, Guan H, Booze RM, Eckman CB, Hersh LB (2004) Estrogen regulates neprilysin activity in rat brain. *Neurosci Lett* **367**, 85-87.

[299] Zhao S, Frotscher M (2010) Go or stop? Divergent roles of Reelin in radial neuronal migration. *Neuroscientist* **16**, 421-434.

[300] Weeber EJ, Beffert U, Jones C, Christian JM, Forster E, Sweatt JD, Herz J (2002) Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. *J Biol Chem* **277**, 39944-39952.

[301] Förster E, Bock HH, Herz J, Chai X, Frotscher M, Zhao S (2010) Emerging topics in Reelin function. *Eur J Neurosci* **31**, 1511-1518.

[302] Hoe H-S, Lee KJ, Carney RSE, Lee J, Markova A, Lee J-Y, Howell BW, Hyman BT, Pak DTS, Bu G, Rebeck GW (2009) Interaction of reelin with amyloid precursor protein promotes neurite outgrowth. *J Neurosci* **29**, 7459-7473.

[303] Hoe H-S, Tran TS, Matsuoka Y, Howell BW, Rebeck GW (2006) DAB1 and Reelin effects on amyloid precursor protein and ApoE receptor 2 trafficking and processing. *J Biol Chem* **281**, 35176-35185.

[304] Beffert U, Morfini G, Bock HH, Reyna H, Brady ST, Herz J (2002) Reelin-mediated signaling locally regulates protein kinase B/Akt and glycogen synthase kinase 3beta. *J Biol Chem* **277**, 49958-49964.

[305] Pujadas L, Rossi D, Andrés R, Teixeira CM, Serra-Vidal B, Parcerisas A, Maldonado R, Giralt E, Carulla N, Soriano E (2014) Reelin delays amyloid-beta fibril formation and rescues cognitive deficits in a model of Alzheimer's disease. *Nat Commun* **5**, 3443.

[306] Kocherhans S, Madhusudan A, Doehner J, Breu KS, Nitsch RM, Fritschy J-M, Knuesel I (2010) Reduced Reelin expression accelerates amyloid-beta plaque formation and tau pathology in transgenic Alzheimer's disease mice. *J Neurosci* **30**, 9228-9240.

[307] Knuesel I, Nyffeler M, Morméde C, Muhia M, Meyer U, Pietropaolo S, Yee BK, Pryce CR, LaFerla FM, Marighetto A, Feldon J (2009) Age-related accumulation of Reelin in amyloid-like deposits. *Neurobiol Aging* **30**, 697-716.

[308] Wirths O, Multhaup G, Czech C, Blanchard V, Tremp G, Pradier L, Beyreuther K, Bayer TA (2001) Reelin in plaques of beta-amyloid precursor protein and presenilin-1 double-transgenic mice. *Neurosci Lett* **316**, 145-148.

[309] Botella-López A, Burgaya F, Gavín R, García-Ayllón MS, Gómez-Tortosa E, Peña-Casanova J, Ureña JM, Del Río JA, Blesa R, Soriano E, Sáez-Valero J (2006) Reelin expression and glycosylation patterns are altered in Alzheimer's disease. *Proc Natl Acad Sci U S A* **103**, 5573-5578.

[310] Cuchillo-Ibañez I, Balmaceda V, Mata-Balaguer T, Lopez-Font I, Sáez-Valero J (2016) Reelin in Alzheimer's disease, increased levels but impaired signaling: When more is less. *J Alzheimers Dis* **52**, 403-416.

[311] Palladino G, Nicolia V, Kovacs GG, Canterini S, Ciraci V, Fuso A, Mangia F, Scarpa S, Fiorenza MT (2017) Sexually dimorphic expression of reelin in the brain of a mouse model of Alzheimer disease. *J Mol Neurosci* **61**, 359-367.

[312] Seripa D, Matera MG, Franceschi M, Daniele A, Bizzarro A, Rinaldi M, Panza F, Fazio VM, Gravina C, D'Onofrio G, Solfrizzi V, Masullo C, Pilotto A (2008) The RELN locus in Alzheimer's disease. *J Alzheimers Dis* **14**, 335-344.

[313] Zhou C, Chao F, Zhang Y, Jiang L, Zhang L, Luo Y, Xiao Q, Chen L, Tang Y (2018) Sex differences in the white matter and myelinated fibers of APP/PS1 mice and the effects of running exercise on the sex differences of AD mice. *Front Aging Neurosci* **10**, 243.

[314] Congdon EE (2018) Sex differences in autophagy contribute to female vulnerability in Alzheimer's disease. *Front Neurosci* **12**, 372.

[315] Webber KM, Bowen R, Casadesus G, Perry G, Atwood CS, Smith MA (2004) Gonadotropins and Alzheimer's disease: The link between estrogen replacement therapy and neuroprotection. *Acta Neurobiol Exp (Warsz)* **64**, 113-118.

[316] Mazure CM, Swendsen J (2016) Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol* **15**, 451-452.

[317] Beery AK (2018) Inclusion of females does not increase variability in rodent research studies. *Curr Opin Behav Sci* **23**, 143-149.

[318] Mielke MM, Ferretti MT, Iulita MF, Hayden K, Khachaturian AS (2018) Sex and gender in Alzheimer's disease – Does it matter? *Alzheimers Dement* **14**, 1101-1103.

[319] Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM (2018) Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement* **14**, 1171-1183.

[320] Canevelli M, Quarata F, Remiddi F, Lucchini F, Lacorte E, Vanacore N, Bruno G, Cesari M (2017) Sex and gender differences in the treatment of Alzheimer's disease: A systematic review of randomized controlled trials. *Pharmacol Res* **115**, 218-223.