Received: 9 December 2022 | Revised: 30 March 2023 | Accepted: 19 April 2023

DOI: 10.1111/jnc.15834

Journal of Neurochemistry JNC The Official Journal of the International Society for Neurochemistry WILEY

REVIEW

Fundamental neurochemistry review: Old brain stories - Influence of age and sex on the neurodegeneration-associated lipid changes

Lorena Cuenca-Bermejo[1,2] | Alessandro Prinetti[2] | Karolina Kublickiene[3] | Valeria Raparelli[4,5] | Alexandra Kautzky-Willer[3] | Colleen M. Norris[6,7] | Louise Pilote[8] | the GOING-FWD Consortium | María Trinidad Herrero[1]

[1]Clinical & Experimental Neuroscience (NiCE), Biomedical Research Institute of Murcia (IMIB- Pascual Parrilla), Institute for Ageing Research (IUIE- EUniWel), University of Murcia, Murcia, Spain

[2]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

[3]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

[4]Department of Translational Medicine, University of Ferrara, Ferrara, Italy

[5]University Center for Studies on Gender Medicine, University of Ferrara, Ferrara, Italy

[6]Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada

[7]Cardiovascular and Stroke Strategic Clinical Network, Alberta Health Services, Edmonton, Alberta, Canada

[8]Division of Clinical Epidemiology, Research Institute of McGill University Health Centre, McGill University, Montreal, Quebec, Canada

Correspondence
Lorena Cuenca-Bermejo, Clinical & Experimental Neuroscience (NiCE), Biomedical Research Institute of Murcia (IMIB- Pascual Parrilla), Institute for Ageing Research (IUIE- EUniWel), University of Murcia, Murcia, Spain.
Email: lorena.cuenca@um.es

Funding information
GENDER-NET Plus ERA-NET Initiative, Grant/Award Number: "La Caixa" Foundation LCF/PR/DE18/52010001, GNP- 161904, GNP-78, Swedish Research Council (2018-00932) and The Austrian Science Fund (FWF, I 4209); Spanish Ministry of Science, Innovation and Universities, Grant/Award Number: FPU 18/02549

Abstract

Brain aging is a naturally occurring process resulting in the decline of cognitive functions and increased vulnerability to develop age-associated disorders. Fluctuation in lipid species is crucial for normal brain development and function. However, impaired lipid metabolism and changes in lipid composition in the brain have been increasingly recognized to play a crucial role in physiological aging, as well as in several neurodegenerative diseases. In the last decades, the role of sexual dimorphism in the vulnerability to develop age-related neurodegeneration has increased. However, further studies are warranted for detailed assessment of how age, sex, and additional non-biological factors may influence the lipid changes in brains. The aim of this work is to address the presence of sex differences in the brain lipid changes that occur along aging, and in the two most common age-related neurodegenerative disorders (Alzheimer's and Parkinson's diseases). We included the studies that assessed lipid-related alterations in the brain of both humans and experimental models. Additionally, we explored the influence of sex on lipid-lowering therapies. We conclude that sex exerts a notable effect on lipid modifications occurring with age and neurodegeneration, and

Abbreviations: 4-HNE, 4-hydroxy-2-nonenal; AA, arachidonic acid; AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid beta precursor protein; Aβ, amyloid beta; CNS, central nervous system; DHA, docosahexaenoic acid; HMG-CoA, 3-hydroxy 3-methylglutaryl coenzyme-A reductase; LDL, low-density lipoprotein; LOAD, late-onset AD; LPO, lipid peroxidation; PC, phosphatidylcholine; PD, Parkinson's disease; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; PSEN, presenilin; PUFA, polyunsaturated fatty acid; SM, sphingomyelin.

in lipid-reducing interventions. Therefore, the application of sex as an experimental variable is strongly encouraged for future research in the field of precision medicine approach.

KEYWORDS
aging, Alzheimer's disease, lipids, Parkinson's disease, sex, statins

1 | BACKGROUND

The continuous increment of worldwide life expectancy has placed age as one of the main risk factors to develop several disorders that impact our societies by means of diseases (Zampino et al., 2022). Among them, neurodegenerative disorders are one of the most common age-related pathologies, being Alzheimer's disease (AD) and Parkinson's disease (PD) the most prevalent and incident ones (Izco et al., 2022). Although considerable advances have been done, the factors initiating and contributing to their pathogenesis are not completely understood. In this line, adequate lipid homeostasis is crucial for brain functions and existing evidence indicates that the disruption of lipid metabolism is a key contributor to different neurodegenerative processes, including dementia, AD, and PD (Chiurchiù et al., 2022; Grassi et al., 2020; Hallett et al., 2019; Kao et al., 2020; McFarlane & Kędziora-Kornatowska, 2019; Moll et al., 2020, 2021; Wong et al., 2017).

Even if the age-related changes do not necessarily promote pathological phenotypes, understanding how the alterations that appear along aging are shared with or can predispose to age-associated diseases can provide key information to improve our quality of life. The interplay among different factors acting in the scenario of aging, including genetics, biological sex, comorbidities, and/or external stressors (e.g., socioeconomic status), is critical to decipher the susceptibility to develop age-related pathologies (Teissier et al., 2020). Existing evidence indicates that biological sex is a modifier (and moderator in some cases) of the most common causes of death and morbidity (Mauvais-Jarvis et al., 2020; Tadiri et al., 2021; Zucker et al., 2021). Unfortunately, its inclusion in preclinical and clinical research still represents an urgent need.

To the best of our knowledge, a narrative review on the impact of biological sex in the brain lipid changes along aging and neurodegenerative-associated processes has not been previously conducted. Therefore, the main objective of this work is to provide a collection of current knowledge regarding this topic. Firstly, we provide an overview of the sex differences in the brain and the main lipid species in the brain, including some examples of lipids and sex differences cross talk. This section is followed by a review and recapitulation of the studies that analyzed the effect of sex on brain lipid changes that occur along physiological aging. We used this same rationale for the two most incident and prevalent age-related neurodegenerative diseases, AD and PD. Finally, we analyzed the influence of sex in lipid-reducing therapies with a focus on neurological events.

2 | BRAIN DIFFERENCES FROM THE SEX PERSPECTIVE

2.1 | Sex and gender concepts

The terms sex and gender are used as equivalent words sometimes in the literature. However, in this review, they are not considered interchangeable terms. Here, the term sex refers to the biological construct, that is, the assignment of biological female/male sex at birth (Slotnick, 2021). We acknowledge that the biological system is not absolutely binary and that additional intersex biological combinations may result from sex chromosome variations, sex hormones, and sexual phenotypes. However, in the following sections, we will refer to biological sex according to the binary system, which represents the majority of individuals included in the experimental works. This biological path starts with (but is not limited to) the sex chromosome complement, which will determine the developmental pathway that culminates in the formation of a gonadal phenotype and primary sex characteristics (McCarthy, 2020). This genetic background is subsequently accompanied by other biological factors, including sex steroids, gene expression programs, or epigenetics, among others (Cerghet et al., 2006; Gamache et al., 2020; Gegenhuber & Tollkuhn, 2020; Hong & Reiss, 2014; McCarthy, 2020; Rosenfeld, 2017).

By contrast, the gender concept considers the social construct: how social norms, roles, and relations determine social identities (Kiely et al., 2019). Some gender-sensitive factors include stress, social roles, education, economic situation, environmental stress like nutrition, and the existence of comorbidities (Mauvais-Jarvis et al., 2020; Mena & Bolte, 2019). A topic of great interest is how sex and gender could determine brain circuits and significantly affect the differential susceptibility to develop neurological disorders (Figure 1). In this review, we just focused on literature referring to the sex concept.

2.2 | Biological sex determines differences in the brain

In mammals, brains of males and females are different at anatomical, structural, cellular, and biochemical levels. The exact mechanisms that drive these differences remain unsolved, but sex steroids are known to play a crucial role in this phenomenon. Sex steroids are cholesterol-derived hormones and they can be grouped into three

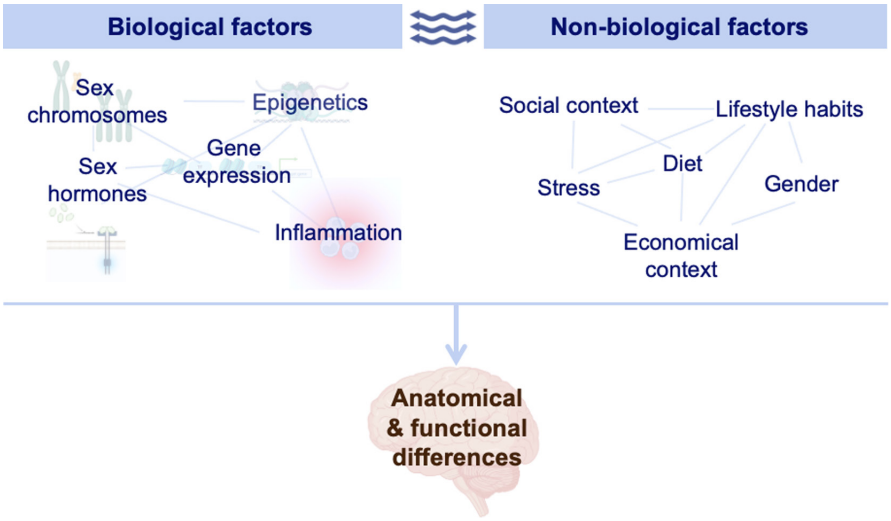


FIGURE 1 The interplay between biological and non-biological factors determines brain anatomy and circuits. Differences between males' and females' brains are stablished during the developmental period because of biological factors, including sex chromosomes and sex hormones. In the following periods of life, different additional biological and non-biological factors contribute to enlarge differences between males' and females' brains. Created with https://biorender.com.

main classes: estrogens, androgens, and progestins (Larson, 2018). Their synthesis is not limited to the gonads; yet, sex hormones can be synthetized in both males and females in extra-gonadal tissues and organs, including several brain areas (Barakat et al., 2016; Hanukoglu et al., 1977; Payne & Hales, 2004). Therefore, the brain can be affected by both, circulating sex hormones and the ones synthetized in situ.

The broad influence of sex hormones in the central nervous system (CNS) is exerted via both genomic (nuclear) and non-genomic (membrane) receptors. These mechanisms do not necessarily exclude each other; instead, they provide an explanation for the sex differences in the sex steroids-mediated neuroprotective effects. The most striking example is the increased risk of women to develop cognitive decline and different neuropathological events associated with the abrupt decline of estrogens during the menopausal transition compared to men (Ancelin et al., 2014; Derby et al., 2009; Duka et al., 2000; Pozzi et al., 2006; Sherwin, 2012). Several works have demonstrated as well an association between reduced testosterone levels and increased risk of AD (Gillett et al., 2003; Moffat et al., 2004; Paoletti et al., 2004); however, the decrease in androgens is less pronounced than one of estrogens in women and testosterone to estrogen conversion may contribute as compensatory mechanism (Maioli et al., 2021). Indeed, it is not clear whether testosterone exerts its neuroprotective effects via its binding to androgen receptors or through its conversion to estrogen is still under debate (Saldanha et al., 2009).

The idea that brain shows sexual dimorphism and that sex steroids have an active role on it was already introduced in the late 1950s (Kolata, 1979; Wallen, 2009). Initial studies using guinea pigs demonstrated that prenatal exposure to steroidal hormones at a specific time period during development was associated with sexual behavior (Phoenix et al., 1959). These findings were later confirmed in other mammalian species, including rodents and non-human primates (Bakker, 2022; Wallen, 2005). Since then, differences between males and females in several brain structures have been demonstrated, such as the hypothalamus (Heck & Handa, 2019; Swaab et al., 2003), the hippocampus (Bowman et al., 2022; Chalangal et al., 2022), the dorsal medial preoptic area (Gorski et al., 1978), the amygdala (Bauer, 2023; McEwen et al., 2016), the frontal cortex (Ginder et al., 2022; Wellman et al., 2020), the thalamus (Poeppl et al., 2016), and the cerebellum (Gao et al., 2022; Oguro et al., 1998). Therefore, besides sexual behavior, sex steroids regulate and contribute to sexual dimorphism of other brain functions, including emotional processing, cognition, motor control, pain, and energy homeostasis (Coyoy et al., 2016; Gorski et al., 1978; Gurvich et al., 2020; Kolata, 1979; Panzica & Melcangi, 2016; Ruigrok et al., 2014).

Accumulating evidence indicates that sex steroids participate and set up sex differences in the brain developmental frame at different levels, including neuronal membrane organization (Baulieu & Robel, 1990), number of neurons (Guillamón et al., 1988), length and density of dendrites and fibers (Rasia-Filho et al., 2012), synapse formation, and neuronal networks (Villa et al., 2016). Furthermore, the influence of sex steroids on sexual dimorphism in the brain is not restricted to the developmental period. Evidence supporting brain anatomical and structural changes across the hormonal fluctuation periods in humans has been recently reviewed (Rehbein et al., 2021), and a relationship between hormonal variations during the estrus cycle and synaptic remodeling was also shown in rodents (Olmos et al., 1989). In the adult brain, sex steroids regulate a plethora of critical processes, which have been summarized in Figure 2. The sex-specific effects and mechanisms of action of sex hormones in these functions are highly dependent on the species (and strain in animal models), treatments, and age, among others.

In addition to their active role in regulating several processes (Figure 2), sex steroids promote sexual dimorphisms in many of them. For example, sex differences have been found in the expression of enzymes involved in γ-aminobutyric acid (GABA) synthesis in the hypothalamus, in the hippocampus, and in the amygdala (McCarthy et al., 2002; Perrot-Sinal et al., 2001). The dopaminergic and noradrenergic systems are additional examples of sexually dimorphic pathways (Kritzer & Creutz, 2008; Thanky et al., 2002; Zachry et al., 2021). The expression of tyrosine hydroxylase in the neurons of the Substantia Nigra, the ventral tegmental area, and the locus

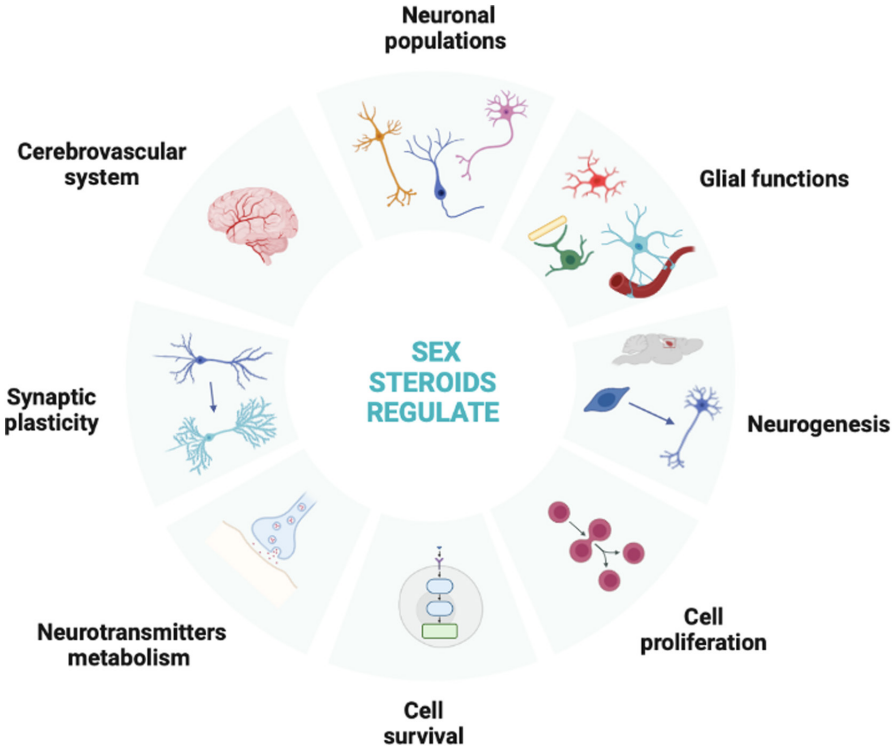


FIGURE 2 Sex steroids regulate a plethora of processes in the nervous system. Sex steroids have been shown to be involved in determining neuronal and glial populations and functions (Chesik & De Keyser, 2010; Gildawie et al., 2020; VanRyzin et al., 2020), synaptic plasticity (Leranth et al., 2004; Wissman et al., 2012), neurogenesis (La Rosa et al., 2021), cell proliferation, and survival (Sohrabji, 2015; Trova et al., 2021), in the synthesis and metabolism of neurotransmitters (Rehbein et al., 2021), and the cerebrovascular system (Duckles & Krause, 2007; Witt & Sandoval, 2014). Created with https://biorender.com.

coeruleus is sex dependent (Brown, Steadman, et al., 2015; Luque et al., 1992; Ma et al., 2007; Thanky et al., 2002). Another sexually dimorphic system is one of the neurotrophic factors in which sex differences have been largely described. In particular, the concentrations, functions, and pathways of the brain-derived neurotrophic factor (BDNF) show a sex-specific pattern (1).

Extensive research has focused on analyzing the role of sex steroids in determining sex differences in the hippocampus. In this brain region, a sex-dependent regulation has been detected in cell proliferation and survival (Barker & Galea, 2008), number and density of dendrites (Mathias et al., 2010; Segarra & McEwen, 1991), patterns and density of fibers (Madeira & Paula-Barbosa, 1993), and neurogenesis (Blankers & Galea, 2021; Duarte-Guterman et al., 2015), among others. In addition, accumulating evidence indicates that the hippocampus is a key player in sex steroid synthesis (Brandt et al., 2020; Gall et al., 2023; Hojo et al., 2009).

These are few of the examples of the extensive influence of sex steroids in the brain which have been extensively described and reviewed in the literature by others (for details, see Chowen et al., 2000; DeCasien et al., 2022; Hansberg-Pastor et al., 2015; Kight et al., 2020; Panzica & Melcangi, 2016; Uhl et al., 2022).

3 | BRAIN LIPIDS

The brain is the most lipid-rich organ and lipids account for at least 50% of its dry weight (Kao et al., 2020; O'Brien & Sampson, 1965; Sastry, 1985). Briefly, the lipid composition of the brain comprises around 50% phospholipids, below 40% glycolipids, and 10% cholesterol (including cholesterol ester and traces of triglycerides). In addition, brain has a very high content of n-3 and n-6 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA) and arachidonic acid (AA) (Skowronska-Krawczyk & Budin, 2020).

In biological membranes, lipids are the principal components that determine the basic architecture, drive the formation of highly organized multimolecular structures, and lead to the creation of multiple and multidimensional levels of order (Sonnino et al., 2014). This concept becomes particularly evident in the nervous system, which possesses a unique lipid composition that allows the high degree of specialized cellular and tissue functions (Aureli et al., 2015). For example, in neurons and in glial cells, the composition of the two plasma membrane monolayers is known to be asymmetric: the inner leaflet is enriched in phosphatidylserine (PS), phosphatidylethanolamine (PE), and phosphatidylinositol (PI), while the outer leaflet is enriched in phosphatidylcholine (PC) and sphingomyelin (SM) (Nelson & Cox, 2017). In addition to this specific composition, lipids in cell membranes continuously undergo rapid changes (e.g., removal and replacement, deacylation/reacylation as well as desialylation/resialylation cycles). These changes are termed as "membrane remodeling" and ensure the adjustments in the chemical structure and molecular shape of the cell membranes (Naudí et al., 2015; Prinetti et al., 2007).

A comprehensive summary of the main types of lipids in the brain, their structure and main functions are listed in Table 1. A clear example of lipids and sex differences cross talk is the fact that cholesterol acts as precursor of sex steroids. Thus, altered cholesterol metabolism can promote detrimental effects on sex steroid functions and, consequently, on brain maintenance. On the other hand, research in animal models indicates that sex steroids in the brain have an active role in modulating lipids' homeostasis since, for example, estrogen modulates lipid trafficking across the blood–brain barrier or de novo fatty acid synthesis (Morselli et al., 2018). Another

line of evidence in the interaction of sex steroids and lipids concerns the induction of the lipid transporter apolipoprotein E (ApoE) isoform 3 by estrogens (Nathan et al., 2004). In the following sections, we will highlight some additional examples, by no means exhaustive, in which the relationship between sex differences and lipids has been evidenced: synaptic transmission, lipid rafts, and lipoxidation.

3.1 | Synaptic transmission and sex steroids

One of the most important singularities of the nervous system is the presence of synaptic transmission. Lipids are essential components of synapses, actively participating in both presynaptic and postsynaptic functions (for an excellent review, please refer to Vallés and Berrantes (2022)). On the one hand, lipids define the biomechanical properties of the cell membranes (e.g., membrane curvature) and dynamics (fluidity and permeability), and compartmentalize anchor synapsis-related proteins (Lauwers et al., 2016). These features are crucial for membrane-bound networks, synaptic vesicle trafficking, neurotransmitter release and reception, ion channel activation and activity, and action potential propagation (Skowronska-Krawczyk & Budin, 2020). On the other hand, lipids, especially phospholipids and inositol lipids, can act as precursors of second messengers (e.g., prostaglandins, endocannabinoids) or act as second messengers themselves (e.g., AA), being involved in synaptic activity and cognitive functions (Hillard, 2018; Sang & Chen, 2006). Thus, it should not be surprising that dysregulation of lipid homeostasis has been related to the development of synaptopathies, loss of synaptic plasticity, and neurological disorders Vallés and Berrantes (2022).

As mentioned in the previous section, sex steroids have been demonstrated to regulate changes in dendritic spine density and fibers distribution in different brain areas, thereby participating in synaptic transmission (Kurz et al., 1986; Mukai et al., 2007; Nilsen & Brinton, 2002; Woolley et al., 1997). In addition, a number of studies indicate that, in addition to regulatory effects, sex steroids are involved in sex differences in synapses (McEwen & Milner, 2017). Two brain areas have received considerable attention in describing the role of sex steroid-receptor signaling in synaptic processes: the hypothalamus and the hippocampus.

Early studies aimed at analyzing sexual dimorphism in brain structures identified the hypothalamus as one of these areas that differed between males and females (Matsumoto & Arai, 1983; Panzica & Melcangi, 2016). Different authors have shown that estrogens mediate the synaptic plasticity in neurons in hypothalamic ventromedial nucleus (Lewis et al., 1995; Sá et al., 2009, 2018). In particular, the effect of estrogens in synaptic organization in this area was found sexually dimorphic in the ventrolateral division of this nucleus: in rats, estrogens induced more dendritic synapses in females and more somatic synapses in males (Sá & Madeira, 2005). In the same study, it was demonstrated that the number of dendritic synapsis changed in parallel with physiological variations in hormonal levels in female rats. When females were at diestrus, sex differences in the number of synapses compared with males were reduced. Thus, these results are of considerable relevance since they highlight the importance of taking the estrous cycle into account when studying sex differences in brain circuits. Sex differences have also been found in the estrogen-dependent organization of serotonergic projections in different hypothalamic sites (Patisaul et al., 2008).

The involvement of sex steroids in hippocampal-related functions with sex-associated differences has been extensively described. Substantial literature suggests that estrogens modulate in a sex-dependent manner hippocampal synapses (McEwen & Milner, 2017). To highlight one example of many, female rats showed a higher number of dendrites and spines on apical dendrites of the hippocampal CA3 cells, whereas males had more apical protrusions (Madeira et al., 1991; Parducz & Garcia-Segura, 1993). A number of studies conducted in experimental models indicate that the regulatory mechanisms of synaptic plasticity are sex dependent. For example, steroids differentially regulated spine synapses in the rat hippocampus. Testosterone can induce as well spine synapses both in the male and female rat hippocampus (Leranth et al., 2004; MacLusky et al., 2006). However, the effect of estrogen was found just for females (Leranth et al., 2003; Lewis et al., 1995; MacLusky et al., 2006). Gall and collaborators (Gall et al., 2023) showed that synaptic plasticity needs cytoskeleton reorganization both in males and females. It was pointed out that synaptic plasticity of hippocampal memory circuits in females, but not in males, acts through membrane-associated estrogen receptor α and requires neuron-derived estrogen (Gall et al., 2023). Conversely, males activate the same downstream kinases relying on NMDA receptor action, independent from estrogen receptor α activation (Romeo et al., 2005).

Besides the hypothalamus and the hippocampus, other brain nuclei show estrogen-dependent spine synapse formation, such as the primary sensory-motor cortex (Chen et al., 2009), the prefrontal cortex (Hao et al., 2007), in the caudal part of the nucleus accumbens (Wissman et al., 2012).

Pertinent to lipid metabolism and sex differences, synaptic transmission in the brain-born is suppressed by estrogen in females but not in males, and this is mediated via inositol triphosphate (IP3) generation and IP3 receptor activation (Huang & Woolley, 2012; Tabatadze et al., 2015).

3.2 | Lipid rafts and sex steroids

Small membrane domains are particularly enriched in specific lipid species, such as cholesterol, sphingolipids, saturated fatty acids, and gangliosides (Grassi et al., 2020; Lingwood & Simons, 2010). This peculiar lipid composition configures intrinsic features that lead to the formation of small dynamic membrane domains known as lipid rafts. These micro- or nano-entities serve as platforms in which proteins can organize multiprotein complexes to favor their interactions at the membrane level and promote signaling cascades (Sonnino & Prinetti, 2012). In this sense, lipid rafts provide an adequate environment for sex hormone signaling via non-genomic pathways. Briefly, in the non-genomic mechanism, sex steroids bind to the cell

TABLE 1 Lipids in the brain and their main functions.

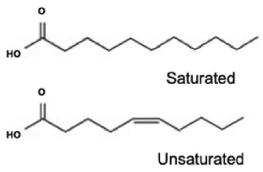
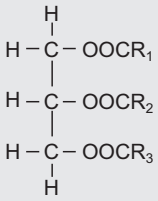
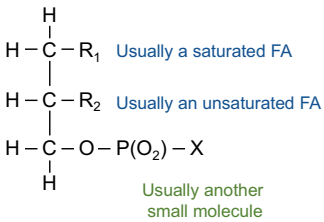
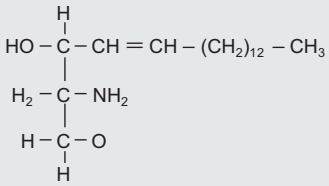
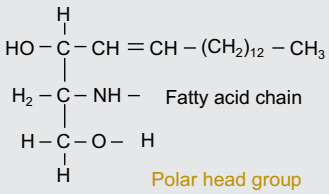
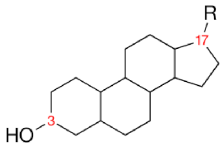
Lipid class	General structure	Examples	Function
FA	Carboxylic acids with hydrocarbonated chains (from 4 to 36 carbon atoms).  Saturated Unsaturated	Docosahexaenoic acid, linoleic acid, and arachidonic acid	Basic building blocks of more complex lipids, source of energy (via β-oxidation), membrane constituents, and regulation of cellular processes (e.g., gene expression) (Fritsche, 2015; Janssen & Kiliaan, 2014)
GL	Long hydrocarbonated chain attached to a glycerol molecule via ester linkages. Each carbon atom of glycerol can be linked to a fatty acid. 	Monoacylglycerol, diacylglycerol, and triglycerides	Membrane formation, cell signaling and vesicle trafficking, energy storage (Almena & Mérida, 2011; Tu-Sekine et al., 2015)
GPL	Two fatty acids linked by an ester bond to the first and second carbon of glycerol, and a polar head group attached to the third carbon by phosphodiester bond  Usually a saturated FA Usually an unsaturated FA Usually another small molecule	Phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol, and cardiolipin. Plasmalogens (pasmenyl ether-phospholipids)	Basic components of cell membrane, regulation of cell processes (e.g., mitophagy), regulation of lipid metabolism (Kay & Grinstein, 2013; Antonny et al., 2015) Basic components of cell membrane, anti-apoptotic properties, regulation of inflammatory processes, and key role in neurodegeneration (Udagawa & Hino, 2022)
SL	Sphingolipid building blocks  **Sphingosine** **Sphingosine**  Fatty acid chain Polar head group **Ceramide** **Ceramide**	Sphingosine-1-phosphate Ceramide Sphingomyelin: phosphatidylcholine as polar head group Neutral glycosphingolipids (cerebrosides and globosides: one or more sugars as polar head group, e.g., glucosylceramide, galactosylceramide) Sulfated galactocerebrosides: esters of galactocerebrosides in which a sulfate group is placed at the C3, e.g., sulfatides Gangliosides: polar head groups contain oligosaccharides and one or more terminal residues of N-acetylneuraminic acid (Neu5Ac), e.g., GM1, GM2, GD1a, and GD1b	Regulation of cell signaling processes (e.g., cell survival) (Bartke & Hannun, 2009; Martin & Sospedra, 2014; Proia & Hla, 2015) Participates in lipid raft formation, regulation of the mitochondrial respiratory chain, and apoptosis (Xu et al., 2010; Mencarelli & Martinez-Martinez, 2013; Castro et al., 2014; Kogot-Levin & Saada, 2014) Major component of myelin (Xicoy et al., 2019) Involved in intracellular transport and cell survival (Mesa-Herrera et al., 2019) Participates in protein trafficking, immune reactions, and neural plasticity (Xiao et al., 2013; Blomqvist et al., 2021) Key role in lipid raft formation, and neurotransmission (Itokazu et al., 2018; Sipione et al., 2020)

TABLE 1 (Continued)

Lipid class	General structure	Examples	Function
Sterols	Steroid nucleus is the basic structure 	Cholesterol and cholesterol esters	Membrane properties (e.g., fluidity), hormones' precursor, lipid raft formation, and signaling processes. (Zhang & Liu, 2015; Kao et al., 2020)

Abbreviations: FA, fatty acids; GL, Glycerolipids; GPL, glycerophospholipids; SL, sphingolipids.

membrane receptors, which localize in lipid rafts domains (Garza-Contreras et al., 2017; Marin & Diaz, 2018). The hormone-receptor complex is able to interact with other membrane proteins (e.g., caveolin-1 or the voltage-dependent anion channel), promoting rapid intracellular signaling cascades (Morselli et al., 2018).

Lipid rafts coordinate both androgen- and estrogen-dependent non-genomic neuroprotective functions in both sexes (Marin & Diaz, 2018; Sarchielli et al., 2021; Spence & Voskuhl, 2012). A recent study conducted in cell cultures indicates that cholesterol in lipid rafts is involved in the expression of membrane androgen receptor and in testosterone-derived neurotoxic effects in an oxidative stress environment (Fadeyibi et al., 2022). Since cholesterol is one of the major components in lipid rafts and participates in steroidogenesis, altered cholesterol metabolism affects not only sex steroids synthesis but also impairs their non-genomic pathways.

3.3 | Lipoxidation and sex differences

Reactive species are essential components in diverse signaling pathways; however, the accumulation of oxidative stress is considered a pivotal mechanism in the aging process as well as in the development of age-related diseases (Calabrese et al., 2008; Moor et al., 2006; Venkateshappa et al., 2012). The imbalance in the redox status with aging toward the accumulation of reactive oxygen and nitrogen species (ROS and RNS, respectively) induces oxidative modifications of proteins, DNA damage, and lipid peroxidation (LPO), thereby causing cell damage (Balaban et al., 2005). Lipids of cell membranes can be easily oxidized by reacting with ROS or by enzymatic reaction with lipoxygenases, cyclooxygenases, and cytochrome P450 (Li et al., 2022). This vulnerability is explained partially by the fact that PUFA residues of membrane lipids are very susceptible to oxidation because of the presence of double bonds (Yin et al., 2011). LPO of PUFAs in cell membranes elevates the endogenous production of aldehydes and reactive carbonyl species such as glyoxal, methylglyoxal, malondialdehyde, and 4-hydroxy-2-nonenal (4-HNE) (Li et al., 2022). Additional lipid species are susceptible to oxidation, such as phospholipids or prostaglandins (Domingues et al., 2013). The resulting toxic byproducts of LPO have the ability to react with other biomolecules, such as proteins, inactivating some antioxidant enzymes (Sottero et al., 2018; Zarrouk et al., 2014). To highlight one example of many, the mitochondrial ATP synthase has been placed as a potential lipoxidative target in human brain aging. As a result of lipoxidative damage, the activity of the mitochondrial ATP synthase is reduced, triggering associated with mitochondrial dysfunction (increased reactive species production), thereby contributing to increased oxidative stress and cell damage (Jové et al., 2019).

The contribution of LPO to aging and age-related neurodegenerative processes has been demonstrated in humans and in experimental models (Cini & Moretti, 1995; Spiteller, 2002). Indeed, the 4-HNE-protein complex can cause autoimmune reactions and has been detected in patients diagnosed with AD, PD, Huntington's disease, and amyotrophic lateral sclerosis (De Virgilio et al., 2016; Di Domenico et al., 2017; Shibata et al., 2011). An emerging research area of sex differences in relation to lipids is lipoxidation. Available evidence from preclinical studies indicates higher LPO levels in males compared to females in advancing (Sobočanec et al., 2003, 2008). The greater neuroprotection in females has been mainly attributed to the sex-dependent regulation of antioxidant enzymes and the neuroprotective effects of estrogens and progesterone (Roof & Hall, 2000; Sobočanec et al., 2003).

4 | BRAIN LIPID COMPOSITION: EFFECT OF SEX ON PHYSIOLOGICAL AGING

In general, the study of brain lipid changes has been done from the perspective of pathological conditions (e.g., Alzheimer's disease) (Phillips et al., 2022). However, aging results from the confluence of time and environmental stressors, creating a scenario of vulnerability that might predispose (or not) to age-related pathologies. Some authors have reviewed the age-associated changes in the brain lipid composition (Naudí et al., 2015; Ooi et al., 2021; Skowronska-Krawczyk & Budin, 2020; Svennerholm et al., 1989, 1991, 1994). However, this topic has never been reviewed using a sex approach. The available studies in which biological sex has been considered as a variable when brain lipids were examined are summarized in Table 2. Most of these investigations have been performed using rodent models, and only few of them have been conducted in humans (Table 2).

TABLE 2 Evidence for the effect of sex in lipid composition in physiological aging, AD, and PD.

Condition	Lipid class	Species	Methodology	References
Physiological aging	Fatty acids	Sprague–Dawley rats	2D-TLC	Galli et al., 1970
		Sprague–Dawley rats	HPLC-MS/MS, GC	Ferdouse et al., 2019
		C57BL/6J mice	UHPLC–MS/MS	Norman et al., 2022
	GPL	BL6/129 Mice	MS	Rappley et al., 2009
		C57BL-6J Mice	MS	Chabrun et al., 2020
		C57Bl/6J mice	HPTLC, GC	Acaz-Fonseca et al., 2017
	SL	C57BL-6J Mice	MS	Chabrun et al., 2020
		C57Bl/6J mice	TQ-MS	Vozella et al., 2017
		Sprague–Dawley rats	HPLC	Palestini et al., 1997
		Human	LC–MS/MS	Couttas et al., 2018
				Song et al., 2022
	Lipid rafts	Human	HPLC	Canerina-Amaro et al., 2017
			TLC, GC	Díaz et al., 2018
Alzheimer's disease	Fatty acids	Mice homozygous for the human *APOE3* or *APOE4* gene	HPLC, LC–MS	Martinsen et al., 2019
	SL	APP^{SL}/PS1Ki mice	TLC, HPTLC	Barrier et al., 2010
		Mice transgenic for APOE3	LC–MS/MS	den Hoedt et al. (2021)
		Human	HPTLC	Kracun et al., 1992
		APP^{SL} and APP^{SL}/PS1 mice	LC–MS	Chan et al., 2012
	Lipid rafts	Human	TLC, GC	Díaz et al., 2018
Parkinson's disease	GPL	Human	HPTLC	Seyfried et al., 2018
	SL	Human	HPTLC	Seyfried et al., 2018

Abbreviations: 2D-TLC, Two-dimensional thin layer chromatography; AD, Alzheimer's disease; GC, gas chromatography; GPL, glycerophospholipids; HPLC, High-Performance Liquid Chromatography; HPLC–MS/MS, High-Performance Liquid Chromatography tandem mass spectrometry; HPTLC, 2D high-performance thin layer chromatography; LC–MS/MS MS, mass spectrometry; PD, Parkinson's disease; SL, sphingolipids; TLC, thin layer chromatography; TQ-MS, triple quadrupole mass spectrometer; UHPLC–MS/MS, Ultra-High-Performance Liquid Chromatography tandem mass spectrometry.

4.1 | Sexual dimorphism in brain fatty acids

Studies showing changes in fatty acids are the most numerous ones. Several works have shown that the fatty acid composition of glycerophospholipids and their unsaturated content is sex specific in rats (Galli et al., 1970; Morselli et al., 2016), whereas others have not (Kitson et al., 2012; Starčević et al., 2017). These diverse results might be because of the different ages of the animals that were analyzed.

Polyunsaturated fatty acids (PUFAs) are essential for normal brain development and function (Ekstrand et al., 2021). PUFAs cannot be synthesized de novo and, therefore, (PUFA) diet intake has a critical role in the brain lipid profile. For example, low dietary consumption of n-3-PUFA has been related to neurodegeneration and increased neuroinflammation (McGrattan et al., 2019; Virmani et al., 2013; Więckowska-Gacek et al., 2021). Importantly, different evidence point out that diet determines in a sex-specific manner in the brain PUFA content (Galli et al., 1970; Jacenik et al., 2021; Morselli et al., 2014, 2016). Furthermore, PUFA content in diet can promote sex-specific behavioral effects. For example, Levant and collaborators demonstrated that postnatal rats (P21-P70) fed with a control diet showed no significant differences in the content of brain DHA, docosapentaenoic acid, and AA of phospholipids when males and females were compared. However, locomotor alterations were detected just in males, despite the fact that variations in the DHA content of the diet resulted in similar changes in the brain LC-PUFA composition in both sexes (Levant et al., 2006).

Oxylipins are oxidized PUFAs that act as bioactive lipids (lipid mediators), participating in crucial cell pathways for brain function in health and disease, such as neuroinflammation (Iliff et al., 2010; Kissoondoyal et al., 2021; Tassoni et al., 2008). Oxylipins profile in rodents has been previously characterized, showing age-related changes: linoleic acid-derived oxylipins are the predominant ones in the developing period, while the ones derived from AA are the most abundant ones in the adult brain (Ferdouse et al., 2019; Hennebelle et al., 2020; Ostermann et al., 2017). In the perinatal period, oxylipins levels did not show differences when males and females were compared, but the effect of the linoleic acid and the 13-hydroxyoctadecadienoic acid on axonal growth was sex specific (Hennebelle et al., 2020). Conversely, in older animals, oxylipins levels were found generally higher in males than in females, with the exception of three particular arachidonic acid-derived oxylipins (9-HETE, 11-HETE, and 15-HETE) whose levels were found higher in

females (Ferdouse et al., 2019; Norman et al., 2022). Interestingly, these sex differences remained unaltered in spite of diet supplementation with PUFA, whereas a higher glucose diet was able to induce sex-specific changes in the oxylipins brain profile (Ferdouse et al., 2019; Norman et al., 2022). Since these sex-specific differences cannot be explained alone by the availability of PUFA, different regulatory mechanisms must underlie. Indeed, sex-related differences were detected in the RNA expression levels of the cytochrome P450 (CYP), an enzyme that participates in the production of oxylipins. Although mRNA levels do not necessarily correspond to enzymatic activity, these results could provide insights into the differential regulatory mechanisms of oxylipin levels in the brain (Gerges & El-Kadi, 2022).

4.2 | Glycerophospholipids

Sex differences have been detected regarding glycerophospholipids composition in the brain. Rappley and collaborators showed that changes in the content of phospholipids along aging were less pronounced in females than in males, and this pattern was similar across brain regions (Rappley et al., 2009). Furthermore, this study revealed significant differences in the lipid composition in the two mice strains used, which were housed under identical conditions, and these divergences were magnified along aging. Therefore, it is of vital importance to consider the experimental model used when it comes to translational comparisons.

A recent metabolomic study conducted in the mouse brain revealed that the presence of several lipid metabolites was sexually dimorphic (Chabrun et al., 2020). Among them, 32 out of 76 of the phosphatidylcholines analyzed were found increased in females' brains compared to males, especially in the brainstem.

On the other hand, a role for estradiol was suggested in the activity of phospholipids methyltransferase (assessed by the incorporation of 3H-methyl group into membrane phospholipids): ovariectomy produced a significant decrease in the enzyme levels, whereas adrenalectomy had no effect on them. Moreover, enzymatic activity appeared to be higher in females than in males (Drouva et al., 1987).

Cardiolipin is a phospholipid crucial for mitochondrial-related functions. To our knowledge, a single work has investigated possible sex differences in this lipid, providing promising findings. In the mouse cortex, the content of unsaturated fatty acids of cardiolipin was higher in males than in females, but the saturation ratio was lower in the former (Acaz-Fonseca et al., 2017). In addition, it was demonstrated that sex steroids regulate the activity of the enzymes involved in the biosynthesis and remodeling of cardiolipin, thereby influencing cardiolipin levels (Acaz-Fonseca et al., 2017).

4.3 | Sphingolipids

Sphingolipids are key components of myelin, especially galactosylceramide, sulfatide, and SM. Studies using brain imaging techniques, both in humans and in experimental models, have evidenced sex-associated differences in the brain white matter content and structure, as well as in oligodendrocytes (Goldstein et al., 2001; Ingalhalikar et al., 2014; Kaczkurkin et al., 2019; Spring et al., 2007). Another line of evidence evaluating sphingolipid content showed that SMs increased in adult females compared to age-matched males (Chabrun et al., 2020). This finding is in line with previous studies reporting sex-related differences in myelin metabolism. For example, levels of myelin-related proteins were found significantly higher in different brain areas (orbitofrontal cortex, corpus callosum, fornix, and spinal cord) when females and males were compared. Conversely, other brain areas (e.g., the dorsal striatum) did not show these differences, suggesting that sexual dimorphism can be found in a region-specific way regarding myelin turnover (Bayless & Daniel, 2015; Cerghet et al., 2006; Ghanem et al., 2017). On the other hand, lysophosphatidylcholines were more prominent in males than in females, a metabolite that has been implicated in myelin sheath degradation (Chabrun et al., 2020).

The hippocampus is one of the brain regions most vulnerable to the aging process. Studies analyzing the sphingolipid profile in this region have found a general increase in these lipids associated with physiological aging, both in mice and in humans (Couttas et al., 2018; Vozella et al., 2017). Some of these changes were found common to both sexes, while others were sex dependent. In particular, the accumulation of sphingolipids containing nervonic acid along aging was more notable in females than in males, particularly for ceramide (d18:1/24:1), hexosylceramide (d18:1/24:1), and SM (d42:2) (Vozella et al., 2017). In humans, the significant accumulation of the different species of sphingolipids was observed just in men (especially in those with N-acyl chains of 16, 22, and 24 carbons) (Couttas et al., 2018). On the contrary, a significant decrease in the ratio of sphingosine-1-phosphate/sphingosine was just detected in elderly women. Indeed, a recent study found that females were susceptible to reduce plasmatic sphingosine-1-phosphate levels in response to exercise, whereas this effect was not observed in age-matched males (Song et al., 2022).

Moreover, levels of sphingolipids can be influenced by diet in a sex-specific manner (Morselli et al., 2014), suggesting that gender-sensitive variables such as exercise or diet can affect the levels of lipids.

Along the adult life, a progressive loss of gangliosides with aging has been reported in human and mouse brains. The trends of variations are very complex and different for different brain areas, glycolipid species, and age ranges (Barrier et al., 2007; Ohsawa & Shumiya, 1991; Svennerholm et al., 1989, 1991, 1994); however, very few detected sex-related differences. Palestini and collaborators found that in young rats, the content of the predominant gangliosides in the brain was higher in females at younger ages, but higher in males in adulthood (Palestini et al., 1997). Therefore, ganglioside changes along aging are sex specific. A subsequent analysis showed that the gangliosides' specific differences when the two sexes were compared were because of the changes in the ceramide moiety. Interestingly, they also discovered that ganglioside composition was

different when the two hemispheres were compared just in females (Palestini et al., 1997).

4.4 | Cholesterol and sterol metabolism

Several enzymes and proteins involved in the sterols metabolism have been found differentially modulated when males and females were compared, such as the 3-hydroxy 3-methylglutaryl coenzyme-A reductase (HMG-CoA), the low-density lipoprotein (LDL) receptor, and the CYP11A1 (Segatto et al., 2013; Watzka et al., 1999). For example, Segatto and colleagues demonstrated age- and sex-related changes in HMG-CoA LDL receptor (Segatto et al., 2013). Among all the brain areas analyzed, the hippocampus and the cortex were the ones showing the most significant differences in rats. They found that these specific changes were independent of estradiol circulating levels, whereas LDL glycosylation might be regulated by this hormone.

4.5 | Lipid rafts

The process of physiological aging is associated with a variety of alterations in brain lipid composition, including the reduction of total lipid content, alterations of polyunsaturated fatty acid content and profile, decreased ganglioside content, and altered sphingoid base composition of sphingolipids (for review, see Ledesma et al. (2012)). Such changes have major effects on the physicochemical properties of lipid rafts (e.g., local membrane microviscosity). Specific alterations in lipid rafts along non- pathological aging have been extensively described in humans and in experimental models (Egawa et al., 2016; Naudí et al., 2015; Grassi et al., 2020; McNamara et al., 2008; Cabré et al., 2018). However, studies exploring sex differences related to the composition and functions of lipid rafts along aging are scarce. The analysis of lipid rafts in the human frontal cortex revealed profound changes when men and women were compared along aging, being those alterations were more pronounced in postmenopausal women (Canerina-Amaro et al., 2017; Díaz et al., 2018; Marin & Diaz, 2018). The major differences in lipid rafts composition were evidenced in reduced levels of total neutral lipids, n-6 PUFAs, and cholesterol, together with increased levels of sulfatides and total polar lipids. The importance of circulating estrogen to preserve lipid rafts has been also reported because of their modulatory role on lipid rafts in postmenopausal women (Marin & Diaz, 2018).

5 | BRAIN LIPID CHANGES: EFFECT OF SEX ON NEURODEGENERATIVE DISEASES

Among the age-related neurodegenerative diseases, Alzheimer's and Parkinson's diseases are the most common ones (Krishnaswami et al., 2020). Thus, the following sections are focused on recapitulating those works in which the effect of sex in the brain lipid changes was considered in both diseases (Table 2).

5.1 | Alzheimer's disease

AD is the most common age-associated neurodegenerative disorder in the world and the main form of dementia. It has a progressive and chronic nature and clinical signs include cognitive dysfunction, memory loss, and behavioral alterations (Scheltens et al., 2021). Its main histopathological features in the brain are the presence of extracellular Aβ plaques and intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau (Chen & Mobley, 2019). The sporadic form of AD is the most common one (>95% of cases) promoted by the interplay of different factors, amongst which age is the leading risk factor. On the contrary, a small proportion of patients show inherited AD associated with genetic variants of three genes: the Aβ precursor protein (APP) and the presenilin genes 1 and 2 (PSEN1 and PSEN2) (Chen & Mobley, 2019; Kloske & Wilcock, 2020). Although the familial form has an early onset, both forms of AD (sporadic and genetic) have a similar clinical picture (disease progression and biomarkers profiles) (Masters et al., 2015).

Approximately, two-thirds of late-onset AD (LOAD) cases are women (Alzheimer's Disease Association, 2021; Bailly et al., 2019; Nebel et al., 2018; Prince et al., 2016). In addition, different works have shown that the progression of the pathology is worse in women than in men (Barnes et al., 2005; Henderson & Buckwalter, 1994; Koran et al., 2017). This was initially attributed to women living longer, but even after adjusting for age, the risk is still increased in women compared to men in >85 years old individuals (Alzheimer's Disease Association, 2021; Dubal, 2020; Mielke et al., 2014). At the same time, it was reported that higher risk for rapid progression and death in early-onset AD is associated with male sex (Claus et al., 1998; Davis et al., 2020; Dubal, 2020; Fernandez & Lapane, 2002; Stern et al., 1997; Ueki et al., 2001). Therefore, it is clear that sex plays a central role in AD, although a clear conclusion has not been reached yet. The contributing factors for these sex-associated differences must be diverse, ranging from biological components (e.g., hormones) to social reasons (e.g., education level, mental health status, stress) (Ferretti et al., 2020; Mielke et al., 2018; Ratnakumar et al., 2019).

A large body of evidence has demonstrated that altered lipid homeostasis is associated with the development and progression of LOAD. In the last decades, this topic has received increasing attention and research has been conducted in this line to understand the fundamental role of lipids in the physiopathology of AD. For example, lipids are key players in Aβ peptide formation as well as in its toxicity (Kao et al., 2020). More specifically, altered lipid raft composition (e.g., high enrichment of GM1 ganglioside in some brain areas) seems to be responsible for disrupting normal APP-dependent signal transduction and pushing APP toward amyloidogenic proteolytic processing via the sequential actions of β- and γ-secretases. In addition, the interaction of newly formed, membrane-bound Aβ interaction with GM1 present at high levels in lipid rafts is a major trigger for the formation of toxic soluble Aβ aggregates and of insoluble amyloid fibrils (Hartmann, 2011). Recently published works collected the brain lipid changes in AD patients and experimental

models of the disease and therefore will not be repeated here (Chew et al., 2020; Kao et al., 2020; Penke et al., 2018; Yin, 2022). Here, we collect those studies that explore lipid-related changes in AD using a sex-disaggregated approach.

5.1.1 | Sex-dependent genetic contributors of AD related to lipid metabolism

In addition to the three genes directly involved in the risk of suffering from AD (i.e., APP, PSEN1, and PSEN2), genome-wide association studies (GWAS) and transcriptome-Wide Association Studies (TWAS) have identified several genes involved in lipid metabolism that constitute AD risk factors (Chew et al., 2020; Dong et al., 2017; El Gaamouch et al., 2016; Hollingworth et al., 2011; Jones et al., 2010; Kunkle et al., 2019). However, we have detected that the sex-related differences in AD linked to these genes have been explored just for two of them, the *APOE* and the *ABCA7* genes.

APOE4

APOE is the gene related to lipid metabolism that has received considerable attention in relation to AD pathology. The E4 isoform of the apolipoprotein E (APOE4) has been firmly stablished as the strongest genetic risk factor for LOAD (Jessica Tulloch et al., 2018). Briefly, the APOE is the principal lipid transporter in the brain, thus it is critical for lipid homeostasis in this organ, especially for cholesterol and phospholipids (Growdon & Hyman, 2014; Wong et al., 2019). It is mainly expressed by astrocytes, although it can also be found in microglia and neurons in a minor proportion (de Chaves & Narayanaswami, 2008; Kloske & Wilcock, 2020; Xu et al., 2006). The APOE gene encodes for three protein isoforms: APOE2, APOE3, and APOE4. In particular, the amino acid sequence of APOE4 provides conformational properties that are associated with reduced lipid transport in the CNS and lead to limited neuronal remodeling and repair (Chew et al., 2020; Frieden et al., 2017; Li et al., 2002; Nguyen et al., 2014).

Compared to other individuals, those homozygous for *APOE4* have approximately a 15-fold higher risk of developing LOAD and even the heterozygous ones show a three-fold increased risk (Chartier-Harlin et al., 1994; de Rojas et al., 2021; Kloske & Wilcock, 2020). Regarding sex differences, carrying the *APOE* ε4 allele (either heterozygous or homozygous) has a higher impact on the development and on the progression of the disease in females compared to males, both in humans and in preclinical models (Altmann et al., 2014; Breitner et al., 1999; Bretsky et al., 1999; Buckley et al., 2019; Hohman et al., 2018; Martinsen et al., 2019; Mortensen & Høgh, 2001; Payami et al., 1996; Ramanan et al., 2019). Different GWAS studies have found that several SNPs associated with APOE and with the lipoprotein metabolism pathway are the highest contributors to LOAD risk, some of them conferring a differential vulnerability to males and females (Altmann et al., 2014; Guo et al., 2017). The interaction between sex and APOE4 is partially explained by the effect of sex hormones; however, the sex-specific effect of APOE4 on AD needs further characterization.

ABCA7

The ATP-binding cassette subfamily A member 7 (ABCA7) has also been identified as an AD-related gene (Hollingworth et al., 2011; Lambert et al., 2013; Steinberg et al., 2015). ABCA7 mediates lipid transport across cell membranes, although its mechanism in the brain is not completely understood (Abe-Dohmae et al., 2004). In AD patients, ABCA7 is involved in the generation, accumulation, and clearance of Aβ peptides (Apostolova et al., 2018; Chan et al., 2008; Fu et al., 2016).

Sex differences have been found in ABCA7 in the context of AD. In mice, suppression of *Abca7* gene promotes differential effects in males and females. In particular, deletion of this gene induces an increment in cholesterol levels in the serum and in the brain in females, while males tend to accumulate other sterols (including derivatives of cholesterol and campesterol) (Fu et al., 2022; Kim et al., 2005). Levels of lipid metabolites, such as lysosphingomyelin, lysophosphatidic acid, or hexosyl-sphingosine, were found similarly altered in both sexes when *Abca7* gene was suppressed (Fu et al., 2022). Interestingly, in the same study, it was found that Aβ42 and Aβ40 levels were changed in a sex-specific manner. *Abca7* KO females showed a reduced cognitive performance compared to males, which was correlated with the cessation of estrous cycling (Logge et al., 2012). Evidence from human trials is aligned with these findings of experimental models. Some works have found that carrying the genetic variants of *ABCA7* related to AD development has a higher impact on women than on men (Nettiksimmons et al., 2016; Prokopenko et al., 2020). For example, from a total of 15 SNPs surrounding the *ABCA7* gene, 10 of them seemed protective for AD risk just in women (Prokopenko et al., 2020). In line with these sex differences, women with reduced estrogen levels and *ABCA7* gene variants showed a higher AD risk (Ratnakumar et al., 2019).

5.1.2 | Altered lipid composition in AD brain from a sex perspective

Fatty acids

Little evidence exists on fatty acid changes in AD from the sex perspective. Martinsen and collaborators found that the brain fatty acid profile and the concentration of different lipid mediators derived from omega-3 acids were affected by age, sex, and APOE genotype (Martinsen et al., 2019). For example, the content of DHA in the cortex of older APOE4 females was reduced if compared to the APOE3 females or the male counterpart.

Sphingolipids

Studies using different experimental models demonstrated that the sphingolipid profile in the cortex showed a sex-specific pattern (Barrier et al., 2010; den Hoedt et al., 2021). In mice, APP^{SL} females (characterized by the presence of Aβ plaques in the frontal cortex) presented decreased levels of ceramides containing saturated fatty acids and increased levels of ceramides containing unsaturated fatty acids compared to APP^{SL} males (Barrier et al.,

2010). Opposite results were found in the AD mouse model based on the APOE4 expression (den Hoedt et al., 2021). Likewise, sex influenced the hippocampal sphingolipid profile in healthy humans carrying the APOE4 genotype (>65 years old): total ceramides, SM, and sulfatides were increased in males but not in females (Couttas et al., 2018). Despite some discrepancies might exist among the different studies, they do not exclude each other. Indeed, they suggest that different pathological mechanisms related to lipid changes might underlie AD pathology.

Different analyses have shown alterations in the ganglioside composition in different brain areas of AD patients (Ariga, 2017; Barrier et al., 2007; Chan et al., 2012; Kracun et al., 1992). In general terms, changes lead to an accumulation of simple gangliosides (e.g., GM2, GM3) and reduction of the complex series (e.g., GM1, GD1a, GD1b) (Kao et al., 2020; Sipione et al., 2020). In the *Abca7* KO mice, a negative correlation between GD1a levels and Aβ42 was in males but not in females. These results are in contrast with previous ones, therefore providing a tool to explore the pathological mechanism of Aβ deposition.

5.1.3 | Lipid rafts

The importance of lipid rafts in AD pathology has been extensively demonstrated, including a central role in Aβ processing and deposition (Arbor et al., 2016; Sonnino et al., 2014). However, how lipid raft alterations contribute to the progression of AD still needs to be clarified. Estrogen signaling occurs in lipid rafts and it is able to regulate lipid raft homeostasis (Canerina-Amaro et al., 2017; Marin et al., 2013; Maselli et al., 2015). Alterations at this level in women have been demonstrated during menopause and in AD, indicating that lipid raft alterations in pathology are also influenced by sex (Marin & Diaz, 2018).

5.2 | Parkinson's disease

PD is a progressive, chronic, age-related neurodegenerative disease. The two principal histopathological hallmarks involved are (i) dopamine depletion (owing to the death of dopaminergic neurons in the *Substantia Nigra pars compacta* (SNpc) and the loss of their terminals in the striatum) and (ii) proteinaceous inclusions (enriched in misfolded α-synuclein) in neuronal cytoplasm, known as Lewy bodies (Cuenca et al., 2018; Poewe et al., 2017). The exact cause of PD still needs to be clarified. Less than 10% of the cases are identified as familial origin (Bloem et al., 2021). However, the majority of cases are the result of the complex interplay among several factors, such as age, genetics and epigenetics, environmental influence, and sex (Kalia & Lang, 2015; Kochmanski et al., 2022; Obeso et al., 2017).

Biological sex has a determinant role in PD at different levels. From an epidemiological perspective, the incidence and prevalence of PD are higher in males than in females (Baldereschi et al., 2000; Wooten et al., 2004). At the clinical level, the symptoms, course of the disease, and the response to medication are also influenced by sex (Bakeberg et al., 2021; Gillies et al., 2014; Haaxma et al., 2007). A recent study has demonstrated that the DNA methylation profile of several core genes of PD pathology is sex specific (Kochmanski et al., 2022). The susceptibility to environmental neurotoxicity in PD patients has also been demonstrated to be associated with sex (Adamson et al., 2022).

Altered lipid homeostasis has received increasing attention as an important contributing factor for PD pathology, having a role in neuronal impairment, altered cell signaling, and in α-synuclein aggregation (Perrin et al., 2000; Ugalde et al., 2019). Recently, several authors have recapitulated the changes in the composition and content of different lipids in PD patients (Galper et al., 2022; Ma et al., 2022; Xicoy et al., 2019). In this section, we review the available evidence showing sex-related differences in the brain lipid changes in PD.

5.2.1 | Sex-dependent genetic contributors of PD related to lipid metabolism

A minor percentage of the cases are directly related to a genetic cause; however, several genetic variants have been identified as contributors to PD pathology (i.e., loci, mutations, SNP variants). In general terms, the genetic contribution in PD can be explained by three types of variations: (i) pathogenic ones, which are variants of genes that are enough to cause the disease (e.g., SNCA, PARK7); (ii) intermediate risk variants, their presence confers a higher risk of developing PD with variable penetrance (e.g., GBA and LRRK2 variants); and (iii) small contribution ones, which are common variants having a low effect size (e.g., variations in SNCA, LRRK2, MAPT) (Galper et al., 2022; Nalls et al., 2019).

Importantly, several works have found that some PD-related genes actively participate in lipid metabolism, such as GBA1 (encoding for glucocerebrosidase), GALC (encoding for galactosylceramidase), SMPD1 (encoding for acid sphingomyelinase), ASAH (encoding for acid ceramidase), SREBF1 (encoding sterol regulatory element binding transcription factor 1), and DGKQ (encoding diacylglycerol kinase theta) (Chang et al., 2017; de Carvalho Guimarães et al., 2012; Do et al., 2011; Galper et al., 2022; Gan-Or et al., 2013; Robak et al., 2017; Simón-Sánchez et al., 2009; Wang et al., 2012). The sex-related differences of these PD genetic risk factors have not been examined for all of them yet.

Different studies have evaluated the role of sex in the susceptibility to carry GBA variants in PD patients, although conflicting results were obtained: some found a male predominance (Neumann et al., 2009; Ortega et al., 2022), while others reported that females were most predominant for PD-GBA (Mata et al., 2008; Setó-Salvia et al., 2012). The reason for these discrepancies might underlie in the cohort size or the geographical location (e.g., Spanish, Brazilian, or Ashkenazi Jewish populations). Importantly, Ortega and collaborators found that even if men were predominant at carrying GBA

variants, females were the predominant sex carrying the most severe GBA variants (Ortega et al., 2022). Whether these variants confer particular features for the disease, still needs to be clarified. In particular, it was demonstrated a male predominance in carrying GBA variants, but females were the predominant sex carrying the most severe GBA variants. Whether these variants confer particular features for the disease still needs to be clarified.

The implication of APOE gene in PD has also received extensive attention and sex component has been proposed. Similar to AD, a significant relationship between the APOE4 genotype and the age-at-onset was found in women but not in men (Buchanan et al., 2007). Sex-related differences in cognitive decline in PD have been reported (Cereda et al., 2016; Reekes et al., 2020). Interestingly, two recent independent studies found that cognitive decline was associated with APOE4 genotype in men with PD (Kim et al., 2021; Tipton et al., 2021). These findings demonstrate a sex-dependent susceptibility to cognitive impairment in PD and have evident clinical implications, although further research should be conducted.

5.2.2 | Altered lipid composition in PD brain from a sex perspective

Recently, several authors have recapitulated the changes in the composition and content of different lipids in PD patients (Galper et al., 2022; Xicoy et al., 2019). The number of studies incorporating sex as an experimental variable in the analysis of changes in the brain lipid composition of PD patients is very low. However, a recent work provided evidence that lipids abnormalities in the SNpc of PD patients were sex specific (Seyfried et al., 2018). Significant changes were found in the PD males' samples for gangliosides, sphingomyelins, and glycerophospholipids (PE and PC) when they were compared with their sex-matched controls. These results were in agreement with those previously described in studies where males and females were grouped (Hadaczek et al., 2015; Riekkinen et al., 1975; Wu et al., 2012). Surprisingly, none of these alterations were detected in the females' samples. Authors suggested that these unexpected data could be attributed to the possibility that males and females were at different clinical stages of the disease, which was not provided. However, a key message emerges from this study: underestimating the effect of biological sex in lipid profiling of the brain might mask important differences that could be crucial to understand the underlying mechanisms of the disease.

Importantly, sex differences have also been evidenced in α-synuclein toxicity. Rappley and collaborators studied the effect of age, sex, and α-synuclein dosage on the glycerophospholipid profile in mouse models of PD. The effect of α-synuclein dosage was very limited compared to the one exerted by physiological aging and sex on the lipid changes observed (Rappley et al., 2009). These findings reinforce the importance of taking into account the sex of the subject: the particular sex-related alterations in the glycerophospholipid environment of cell membranes might induce different changes in α-synuclein metabolism that might explain sexual differences in PD.

6 | NEUROLOGICAL EFFECTS OF LIPID-REDUCING THERAPIES AND SEX DIFFERENCES

The family of lipid-lowering drugs includes statins, inhibitors of cholesterol absorption (e.g., ezetimibe), proprotein convertase subtilisin/kexin (PCSK) 9-inhibitors (e.g., evolocumab and alirocumab) niacin or fibrates (Ruscica et al., 2021). Among them, the use of statins is very extended around the world to reduce the risk associated with cardiovascular diseases (Gaudet et al., 2017). Their action is based on the inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and they are very effective in reducing serum cholesterol levels (Fadeyibi et al., 2022). A number of works have proven that lipid-reducing therapies are able to modulate the development of neurological diseases (Kosowski et al., 2021) and research to understand their efficacy in the prevention and treatment of neurodegenerative diseases has considerably increased in the last years (Kosowski et al., 2021; Kuang, 2020; Samant & Gupta, 2021). However, this has been a topic of debate since the available results from clinical trials are very ambiguous concerning the use of statins and other lipid-reducing drugs to prevent or treat neurodegenerative disorders. Some clinical and preclinical studies have demonstrated beneficial effects of lipid-lowering therapies in dementia, AD, and PD (Rockwood & Darvesh, 2003; Wolozin et al., 2000; Yan et al., 2011, 2014). For example, the use of statins was associated with improvement in cognitive decline (Schultz et al., 2018), the reduced risk of statin users to develop AD (Samant & Gupta, 2021), or the reduction in the motor symptoms progression in PD (Jeong et al., 2021). A number of mechanisms have been proposed to explain the neuroprotective and therapeutical effects in the CNS of the lipid-lowering agents, such as their anti-inflammatory and anti-thrombotic properties, the ability to induce neuronal plasticity and modulate neurotransmission, and the inhibition of Aβ production (Dai et al., 2021; Simons et al., 2001). Conversely, others have not found significant contribution of statins in the neurodegenerative process (Rea et al., 2005) or have described harmful effects (Dai et al., 2021; Jeong et al., 2021; Pasha et al., 2022; Schultz et al., 2018). Altogether, these evidence point out that statins might have both positive and detrimental effects on the nervous system, which can be ascribed to different factors (e.g., severity of disease, type and dose of statins, variable indicators to evaluate the outcome, duration of treatment, ethnicity, etc.) (Karimi et al., 2023; Ruscica et al., 2021; Shepardson et al., 2011).

Similar to other scenarios, clinical trials to evaluate the safety and efficacy of lipid-lowering therapies have been predominantly performed in men (Faubion et al., 2019; Khan et al., 2020). Therefore, the current clinical guidelines barely consider the sex variable in the use of lipid-reducing agents as clinical interventions. Mercuro and collaborators collected evidence regarding differences in the effect

TABLE 3 Studies evidencing sex differences in the effects of lipid-lowering therapies.

Reference	Research strategy	Intervention details	Main results
Karimi et al. 2023	Multicenter control–case study	*Participants*: 1917 (34.8% women) *Inclusion criteria*: premature coronary artery disease *Treatment*: atorvastatin, lovastatin, rosuvastatin, simvastatin	LDL levels control: Lovastatin, rosuvastatin, simvastatin – women < men Atorvastatin – no significant differences
Paquette et al. 2023	Follow-up of clinical reports	*Participants*: 259 (38% women) *Inclusion criteria*: patients treated *Treatment*: PCSK9 inhibitors	Relative change of LDL levels was significantly higher in men > women Menopausal status did not affect statin efficacy
Olmastroni et al. (2020, b)	Statistical analysis from national administrative databases (Italy)	*Participants*: 613654 (50.6% women) *Inclusion criteria*: patients under statin treatment for 5 years. *Treatment*: rosuvastatin, simvastatin, pravastatin lovastatin, lovastatin, atorvastatin	More side effects reported in women
Wu et al. 2020	Clinical follow-up	*Participants*: 158 (31.6% women) *Inclusion criteria*: patients percutaneous coronary intervention + statin treatment. Follow-up ~1 year *Treatment*: atorvastatin	Higher decrease in women > men in triglycerides, LDL, and ApoB levels
Dagliati et al. (2021)	Large-scale cohort using the UK Biobank and statistical modeling	*Participants*: 252327 (54.2% women) *Inclusion criteria*: statin users. Follow-up: medical visits *Treatment*: simvastatin, atorvastatin, pravastatin, rosuvastatin	Higher survival rates in men treated with statins (compared to women)
Nanna et al. (2018)	Statistical comparison of the PALM registry	*Participants*: 5693 (43% women) *Inclusion criteria*: patients ≤75 and >75 years old who were eligible for primary or secondary prevention statin use *Treatment*: statin type not specified	More side effects reported in women
Sabatine et al. 2017	Randomized, double-blind, placebo-controlled trial	*Participants*: 27564 (24.6% women) *Inclusion criteria*: participants with atherosclerotic cardiovascular disease and LDL cholesterol levels ≥70 mg/dL receiving statin therapy. Follow-up ~2.2 years *Treatment*: evolocumab (PCSK9 inhibitor) + statin therapy	No sex differences in the efficacy of treatments
Zissimopoulos et al. 2017[a]	Examination of medical and pharmacy claims	*Participants*: 399979 (60.3% women) *Inclusion criteria*: statin users (2006–2013), high or low exposure to statins. Follow-up time ~7.2 years *Treatment*: simvastatin, atorvastatin, pravastatin, rosuvastatin	Sex-related differences in the AD risk depending on the statin molecule
Hsue et al. 2015	Comparison of six large randomized clinical trials using patient-level data	*Participants*: 39173 (23.4% women) *Inclusion criteria*: randomized clinical trials using data from patients following statin treatments. Follow-up ~4–5 years *Treatment*: atorvastatin at high and low doses	Higher unwanted side effects in women: myalgia (at lower doses) and elevation of hepatic enzymes (at higher doses) No sex differences in the efficacy of treatments More side effects reported in women

[a] Studies in which neurological effects were explored.

of lipid-lowering therapies in men and women (Mercuro et al., 2011). Here, we provide a list of trials that were released after their publication in which studies have explored the pharmacological properties and the effect of lipid-lowering drugs applying the sex disaggregation (Table 3). Collectively, these evidence do not allow us to reach consistent conclusions, and research in this line should be expanded to create specific guidelines and recommendations. Extensive research has concluded that women show less adherence to statin therapy or have less likely to be prescribed statins (Olmastroni et al., 2020, b; Peters et al., 2018; Zhao et al., 2020). In this line, a roundtable pointed out that considering sex and gender is crucial to reach conclusions regarding the use of lipid-lowering therapies. They analyzed a series of studies and two relevant points can be highlighted from it. The first one concerns the underrepresentation of women because of the assumed social roles: authors claimed that, compared to single or divorced women, the married ones had less participation in clinical

trials because they assume that they have to provide everyone's care but themselves. The second idea relies on the evidence that women are more prone to develop new or worse side effects compared to men, possibly owing to the fact that some comorbidities are more frequent in women than in men (e.g., hypothyroidism), which can be exacerbated by statin use (Brown and Mackey et al., 2015).

Few studies have explored the sex differences in the neurological outcomes associated with lipid-lowering therapies. Indeed, we found just one trial matching these premises (Table 3) (Zissimopoulos et al., 2017). A recent preclinical study investigated the possible neuroprotective action of atorvastatin after the induction of cerebral microhemorrhages (Bergeron et al., 2021). Strikingly, authors found that atorvastatin improved visuospatial memory in males but not in females. The mechanisms involved in these differences need to be clarified in the future research.

7 | CONCLUDING REMARKS

Sex differences have been observed in both brain and in lipid metabolism, including the neuroscience field. However, the majority of studies have not investigated possible sex differences in the experimental design. To the author's knowledge, this narrative review is the first one that recapitulates the evidence of the sex and gender effect on brain lipid changes along aging and in age-related neurodegenerative disease.

Along this research, we have observed that the inclusion of the female sex in biomedical studies is tending to increase in the last decades. Sex-related differences have been demonstrated in several lipid classes, including fatty acids, phospholipids, sphingomyelin, or gangliosides, among others. However, because of the few available data, it is not possible to stablish a consensus regarding the exact role of sex on the lipid alterations along aging and neurodegeneration, and neither for the underlying mechanisms in those sex differences. Noteworthy, even if scarce, the findings observed are promising to further characterize the sex-dependent changes and explore the functional consequences associated with them. In this sense, the application of omics is of special relevance in this area, since they are key to provide insights into small variances that cannot be detected with conventional techniques.

Analyzing the influence of sex adds some complexity to the experimental design; however, not including these variables is associated with biased results. Thus, previous works involving a mixed sample of both sexes are encouraged to re-examine their data if possible and check whether sex-related differences might appear. The study of lipid modifications in physiology and pathology paying attention to sex is a promising area of research and future research will benefit from it. As demonstrated in this review, most of our knowledge on this topic is limited to the description of differences in the lipid composition or lipid-related genes. By contrast, little evidence exists regarding the biological meaning of these findings remains unclear.

Importantly, sex differences in the brain are not limited to sex steroids and involve many other factors, such as epigenetics or gender (Forger, 2016; Peedikayil-Kurien et al., 2022). In particular, we observed that research accounting for the gender effect is very limited and does not allow us to reach consistent conclusions. At this point, it is worthy to mention that gender comprises the social context, economic, or education, among others, which also affects brain development, functions, and vulnerability to disease. Thus, considering these variables may contribute to a better representation of the real practical scenario. On the one hand, it will allow us to understand the differential susceptibility of men and women to different neurological diseases. On the other hand, it could be extremely helpful to inspire early diagnostic tools and design effective therapeutical strategies.

Altogether, the present work evidences the existence of sex-associated lipid changes in the brain in humans and in preclinical models, as well as in their response to lipid-lowering therapies. We conclude that sex is an important variable to take into account in the study of brain lipid changes and that sex steroids play a key role.

AUTHOR CONTRIBUTIONS

Conception and design: L.C.-B., A.P., M.T.H. Data collection and curation: L.C.-B. Investigation: L.C.-B. Validation and supervision: A.P., M.T.H. Writing original draft: L.C.-B. Writing-Review and editing: L.C.-B., A.P., K.K., V.R., A.K.-W., C.M.N., M.T.H. Funding acquisition: L.C.-B., K.K., V.R., A.K.-W., C.M.N., M.T.H. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The GOING-FWD Consortium is funded by the GENDER-NET Plus ERA-NET Initiative (Project Ref. Number: GNP-78): "La Caixa" Foundation (ID 100010434) with code LCF/PR/DE18/52010001, The Canadian Institutes of Health Research (GNP- 161904), The Swedish Research Council (2018-00932) and The Austrian Science Fund (FWF, I 4209). This work was supported by the Spanish Ministry of Science, Innovation and Universities grant FPU 18/02549 to Cuenca-Bermejo L. Authors would like to acknowledge MAGM and MCIG for administrative assistance. Authors thank to reviewers and editorial comments.

CONFLICT OF INTEREST STATEMENT

A.P. is the Treasurer of the International Society for Neurochemistry.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.15834.

DATA AVAILABILITY STATEMENT

No data are available.

ORCID

Lorena Cuenca-Bermejo https://orcid.org/0000-0003-1589-2139
Alessandro Prinetti https://orcid.org/0000-0003-0252-2593
Karolina Kublickiene https://orcid.org/0000-0002-4841-6836

REFERENCES

Abe-Dohmae, S., Ikeda, Y., Matsuo, M., Hayashi, M., Okuhira, K. I., Ueda, K., & Yokoyama, S. (2004). Human ABCA7 supports

apolipoprotein-mediated release of cellular cholesterol and phospholipid to generate high density lipoprotein. *The Journal of Biological Chemistry*, *279*, 604–611.

Acaz-Fonseca, E., Ortiz-Rodriguez, A., Lopez-Rodriguez, A. B., Garcia-Segura, L. M., & Astiz, M. (2017). Developmental sex differences in the metabolism of cardiolipin in mouse cerebral cortex mitochondria. *Scientific Reports*, *7*, 43878. https://doi.org/10.1038/srep43878

Adamson, A., Buck, S. A., Freyberg, Z., & De Miranda, B. R. (2022). Sex differences in dopaminergic vulnerability to environmental toxicants—implications for Parkinson's disease. *Current Environmental Health Reports*, *9*(4), 563–573.

Almena, M., & Mérida, I. (2011). Shaping up the membrane: Diacylglycerol coordinates spatial orientation of signaling. *Trends in Biochemical Sciences*, *36*(11), 593–603. https://doi.org/10.1016/j.tibs.2011.06.005

Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. *Annals of Neurology*, *75*, 563–573.

Alzheimer's disease Association. (2021). 2021 Alzheimer's disease facts and figures. *Alzheimer's Dement*, *17*, 327–406.

Ancelin, M. L., Ripoche, E., Dupuy, A. M., Samieri, C., Rouaud, O., Berr, C., Carrière, I., & Ritchie, K. (2014). Gender-specific associations between lipids and cognitive decline in the elderly. *European Neuropsychopharmacology*, *24*, 1056–1066.

Antonny, B., Vanni, S., Shindou, H., & Ferreira, T. (2015). From zero to six double bonds: phospholipid unsaturation and organelle function. *Trends in Cell Biology*, *25*(7), 427–436. https://doi.org/10.1016/j.tcb.2015.03.004

Apostolova, L. G., Risacher, S. L., Duran, T., Stage, E. C., Goukasian, N., West, J. D., Do, T. M., Grotts, J., Wilhalme, H., Nho, K., Phillips, M., Elashoff, D., Saykin, A. J., & Alzheimer's Disease Neuroimaging Initiative. (2018). Associations of the Top 20 Alzheimer disease risk variants with brain amyloidosis. *JAMA Neurology*, *75*(3), 328–341. https://doi.org/10.1001/jamaneurol.2017.4198

Arbor, S. C., Lafontaine, M., & Cumbay, M. (2016). Amyloid-beta Alzheimer targets — Protein processing, lipid rafts, and amyloid-beta pores. *The Yale Journal of Biology and Medicine*, *89*, 5–21.

Ariga, T. (2017). *The pathogenic role of ganglioside metabolism in Alzheimer's disease-cholinergic neuron-specific gangliosides and neurogenesis*. Humana Press Inc.

Aureli, M., Grassi, S., Prioni, S., Sonnino, S., & Prinetti, A. (2015). Lipid membrane domains in the brain. *Biochimica et Biophysica Acta*, *1851*, 1006–1016.

Bailly, L., David, R., Chevrier, R., Grebet, J., Moncada, M., Fuch, A., Sciortino, V., Robert, P., & Pradier, C. (2019). Alzheimer's disease: Estimating its prevalence rate in a French geographical unit using the National Alzheimer Data Bank and national health insurance information systems. *PLoS One*, *14*, e0216221.

Bakeberg, M. C., Gorecki, A. M., Kenna, J. E., Jefferson, A., Byrnes, M., Ghosh, S., Horne, M. K., McGregor, S., Stell, R., Walters, S., Chivers, P., Winter, S. J., Mastaglia, F. L., & Anderton, R. S. (2021). Differential effects of sex on longitudinal patterns of cognitive decline in Parkinson's disease. *Journal of Neurology*, *268*, 1903–1912.

Bakker, J. (2022). The role of steroid hormones in the sexual differentiation of the human brain. *Journal of Neuroendocrinology*, *34*, 1–11.

Balaban, R. S., Nemoto, S., & Finkel, T. (2005). Mitochondria, oxidants, and aging.

Baldereschi, M., Di Carlo, A., Rocca, W. A., Vanni, P., Maggi, S., Perissinotto, E., Grigoletto, F., Amaducci, L., & Inzitari, D. (2000). Parkinson's disease and parkinsonism in a longitudinal study: Two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. *Neurology*, *55*, 1358–1363.

Barakat, R., Oakley, O., Kim, H., Jin, J., & Ko, C. M. J. (2016). Extra-gonadal sites of estrogen biosynthesis and function.

Barker, J. M., & Galea, L. A. M. (2008). Repeated estradiol administration alters different aspects of neurogenesis and cell death in the hippocampus of female, but not male, rats. *Neuroscience*, *152*, 888–902.

Barnes, L. L., Wilson, R. S., Bienias, J. L., Schneider, J. A., Evans, D. A., & Bennett, D. A. (2005). Sex differences in the clinical manifestations of Alzheimer disease pathology. *Archives of General Psychiatry*, *62*, 685.

Barrier, L., Ingrand, S., Damjanac, M., Rioux, B. A., Hugon, J., & Page, G. (2007). Genotype-related changes of ganglioside composition in brain regions of transgenic mouse models of Alzheimer's disease. *Neurobiology of Aging*, *28*, 28–1872.

Barrier, L., Ingrand, S., Fauconneau, B., & Page, G. (2010). Gender-dependent accumulation of ceramides in the cerebral cortex of the APPSL/PS1Ki mouse model of Alzheimer's disease. *Neurobiology of Aging*, *31*, 1843–1853.

Bartke, N., & Hannun, Y. A. (2009). Bioactive sphingolipids: Metabolism and function. *Journal of Lipid Research*, *50* Suppl(Suppl), S91–S96. https://doi.org/10.1194/jlr.R800080-JLR200

Bauer, E. P. (2023). Sex differences in fear responses: Neural circuits. *Neuropharmacology*, *222*, 109298.

Baulieu, E. E., & Robel, P. (1990). Neurosteroids: A new brain function? *The Journal of Steroid Biochemistry and Molecular Biology*, *37*, 395–403.

Bayless, D. W., & Daniel, J. M. (2015). Sex differences in myelin-associated protein levels within and density of projections between the orbital frontal cortex and dorsal striatum of adult rats: Implications for inhibitory control. *Neuroscience*, *300*, 286–296.

Bergeron, S., Barus, R., Leboullenger, C., Auger, F., Bongiovanni, A., Tardivel, M., Jonneaux, A., Laloux, C., Potey, C., Bordet, R., Chen, Y., & Gautier, S. (2021). Beneficial effects of atorvastatin on sex-specific cognitive impairment induced by a cerebral microhaemorrhage in mice. *British Journal of Pharmacology*, *178*, 1705–1721.

Blankers, S. A., & Galea, L. A. M. (2021). Androgens and adult neurogenesis in the hippocampus. *Androgens: Clinical Research and Therapeutics*, *2*(1), 203–215.

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *Lancet*, *397*, 2284–2303.

Blomqvist, M., Zetterberg, H., Blennow, K., & Månsson, J. E. (2021). Sulfatide in health and disease. The evaluation of sulfatide in cerebrospinal fluid as a possible biomarker for neurodegeneration. *Molecular and Cellular Neuroscience*. https://doi.org/10.1016/j.mcn.2021.103670

Bowman, R., Frankfurt, M., & Luine, V. (2022). Sex differences in cognition following variations in endocrine status. *Learning & Memory*, *29*(9), 234–245.

Brandt, N., Fester, L., & Rune, G. M. (2020). Neural sex steroids and hippocampal synaptic plasticity. *Vitamins and Hormones*, *114*, 125–143.

Breitner, J. C., Wyse, B. W., Anthony, J. C., Welsh-Bohmer, K. A., Steffens, D. C., Norton, M. C., Tschanz, J. T., Plassman, B. L., Meyer, M. R., Skoog, I., & Khachaturian, A. (1999). APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: The Cache County Study. *Neurology*, *53*(2), 321–331. https://doi.org/10.1212/wnl.53.2.321

Bretsky, P. M., Buckwalter, J. G., Seeman, T. E., Miller, C. A., Poirier, J., Schellenberg, G. D., Finch, C. E., & Henderson, V. W. (1999). Evidence for an interaction between apolipoprotein E genotype, gender, and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *13*, 216–221.

Brown, E. C. Z., Steadman, C. J., Lee, T. M., Padmanabhan, V., Lehman, M. N., & Coolen, L. M. (2015). Sex differences and effects of prenatal exposure to excess testosterone on ventral tegmental area dopamine neurons in adult sheep. *The European Journal of Neuroscience*, *41*, 1157–1166.

Brown, W. V., Mackey, R. H., Orringer, C. E., & Pearson, T. A. (2015). JCL roundtable: Gender differences in reduction of CVD in response

to lipid-lowering drugs, in J. *Journal of Clinical Lipidology*, *9*(5), 624–633.

Buchanan, D. D., Silburn, P. A., Prince, J. A., & Mellick, G. D. (2007). Association of APOE with Parkinson disease age-at-onset in women. *Neuroscience Letters*, *411*, 185–188.

Buckley, R. F., Mormino, E. C., Rabin, J. S., Hohman, T. J., Landau, S., Hanseeuw, B. J., Jacobs, H. I. L., Papp, K. V., Amariglio, R. E., Properzi, M. J., Schultz, A. P., Kirn, D., Scott, M. R., Hedden, T., Farrell, M., Price, J., Chhatwal, J., Rentz, D. M., Villemagne, V. L., … Sperling, R. A. (2019). Sex differences in the association of global amyloid and regional tau Deposition Measured by positron emission tomography in clinically Normal older adults. *JAMA Neurology*, *76*, 76.

Cabré, R., Naudí, A., Dominguez-Gonzalez, M., Jové, M., Ayala, V., Mota-Martorell, N., Pradas, I., Nogueras, L., Rué, M., Portero-Otín, M., Ferrer, I., & Pamplona, R. (2018). Lipid profile in human frontal cortex is sustained throughout healthy adult life span to decay at advanced ages. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *73*(6), 703–710.

Calabrese, V., Butterfield, D. A., & Stella, A. M. G. (2008). Aging and oxidative stress response in the CNS, in Handb. In *Neurochemistry and molecular neurobiology* (pp. 103–146). Springer. https://doi.org/10.1007/978-0-387-32671-9_6

Canerina-Amaro, A., Hernandez-Abad, L. G., Ferrer, I., Quinto-Alemany, D., Mesa-Herrera, F., Ferri, C., Puertas-Avendaño, R. A., Diaz, M., & Marin, R. (2017). Lipid raft ER signalosome malfunctions in menopause and Alzheimer's disease. *Frontiers in Bioscience—Scholar*, *9*, 111–126.

Castro, B. M., Prieto, M., & Silva, L. C. (2014). Ceramide: A simple sphingolipid with unique biophysical properties. *Progress in Lipid Research*, *54*, 53–67. https://doi.org/10.1016/j.plipres.2014.01.004

Cereda, E., Cilia, R., Klersy, C., Siri, C., Pozzi, B., Reali, E., Colombo, A., Zecchinelli, A. L., Mariani, C. B., Tesei, S., Canesi, M., Sacilotto, G., Meucci, N., Zini, M., Isaias, I. U., Barichella, M., Cassani, E., Goldwurm, S., & Pezzoli, G. (2016). Dementia in Parkinson's disease: Is male gender a risk factor? *Parkinsonism and Related Disorders*, *26*, 67–72.

Cerghet, M., Skoff, R. P., Bessert, D., Zhang, Z., Mullins, C., & Ghandour, M. S. (2006). Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents. *The Journal of Neuroscience*, *26*, 1439–1447.

Chabrun, F., Dieu, X., Rousseau, G., Chupin, S., Letournel, F., Procaccio, V., Bonneau, D., Lenaers, G., Simard, G., Mirebeau-Prunier, D., Chao de la Barca, J. M., & Reynier, P. (2020). Metabolomics reveals highly regional specificity of cerebral sexual dimorphism in mice. *Progress in Neurobiology*, *184*, 101698.

Chalangal, J., Mazid, S., Windisch, K., & Milner, T. A. (2022). Sex differences in the rodent hippocampal opioid system following stress and oxycodone associated learning processes. *Pharmacology, Biochemistry, and Behavior*, *212*, 173294.

Chan, R. B., Oliveira, T. G., Cortes, E. P., Honig, L. S., Duff, K. E., Small, S. A., Wenk, M. R., Shui, G., & Di Paolo, G. (2012). Comparative lipidomic analysis of mouse and human brain with Alzheimer disease. *The Journal of Biological Chemistry*, *287*, 2678–2688.

Chan, S. L., Kim, W. S., Kwok, J. B., Hill, A. F., Cappai, R., Rye, K. A., & Garner, B. (2008). ATP-binding cassette transporter A7 regulates processing of amyloid precursor protein in vitro. *Journal of Neurochemistry*, *106*, 793–804.

Chang, D., Nalls, M. A., Hallgrímsdóttir, I. B., Hunkapiller, J., van der Brug, M., Cai, F., International Parkinson's Disease Genomics Consortium, Me Research Team, Kerchner, G. A., Ayalon, G., Bingol, B., Sheng, M., Hinds, D., Behrens, T. W., Singleton, A. B., Bhangale, T. R., & Graham, R. R. (2017). A meta analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nature Genetics 49*, 1511, 1516.

Chartier-Harlin, M. C., Parfitt, M., Legrain, S., Pérez-Tur, J., Brousseau, T., Evans, A., Berr, C., Vidal, O., Roques, P., & Gourlet, V. (1994). Apolipoprotein E, epsilon 4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13.2 chromosomal region. *Human Molecular Genetics*, *3*(4), 569–574.

Chen, J. R., Yan, Y. T., Wang, T. J., Chen, L. J., Wang, Y. J., & Tseng, G. F. (2009). Gonadal hormones modulate the dendritic spine densities of primary cortical pyramidal neurons in adult female rat. *Cerebral Cortex*, *19*, 2719–2727.

Chen, X. Q., & Mobley, W. C. (2019). Alzheimer disease pathogenesis: Insights from molecular and cellular biology studies of oligomeric Aβ and tau species. *Frontiers in Neuroscience*, *13*, 659.

Chesik, D., & De Keyser, J. (2010). Progesterone and dexamethasone differentially regulate the IGF-system in glial cells. *Neuroscience Letters*, *468*, 178–182.

Chew, H., Solomon, V. A., & Fonteh, A. N. (2020). Involvement of lipids in Alzheimer's disease pathology and potential therapies. *Frontiers in Physiology*, *11*, 598. https://doi.org/10.3389/fphys.2020.00598

Chiurchiù, V., Tiberi, M., Matteocci, A., Fazio, F., Siffeti, H., Saracini, S., Mercuri, N. B., & Sancesario, G. (2022). Lipidomics of bioactive lipids in Alzheimer's and Parkinson's diseases: Where are we? *International Journal of Molecular Sciences*, *23*(11), 6235. https://doi.org/10.3390/ijms23116235

Chowen, J. A., Azcoitia, I., Cardona-Gomez, G. P., & Garcia-Segura, L. M. (2000). Sex steroids and the brain: Lessons from animal studies. *Journal of Pediatric Endocrinology & Metabolism*, *13*, 1045–1066.

Cini, M., & Moretti, A. (1995). Studies on lipid peroxidation and protein oxidation in the aging brain. *Neurobiology of Aging*, *16*, 53–57.

Claus, J. J., Gool, W. A., Van, T. S., Walstra, G. J. M., Kwa, V. I. H., Hijdra, A., Verbeeten, B., Koelman, J. H. T. M., Bour, L. J., & Ongerboer De Visser, B. W. (1998). Predicting survival in patients with early Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *9*, 284–293.

Couttas, T. A., Kain, N., Tran, C., Chatterton, Z., Kwok, J. B., & Don, A. S. (2018). Age-dependent changes to sphingolipid balance in the human hippocampus are gender-specific and May sensitize to neurodegeneration. *Journal of Alzheimer's Disease*, *63*, 503–514.

Coyoy, A., Guerra-Araiza, C., & Camacho-Arroyo, I. (2016). Metabolism regulation by estrogens and their receptors in the central nervous system before and after menopause. *Hormone and Metabolic Research*, *48*, 489–496.

Cuenca, L., Gil-Martínez, A. L., Cano-Fernandez, L., Sanchez-Rodrigo, C., Estrada, C., & Fernandez-Villalba, E. H. M. T. (2018). Parkinson's disease: A short story of 200 years. *Histology and Histopathology*, *12*, 18073.

Dagliati, A., Peek, N., Brinton, R. D., & Geifman, N. (2021). Sex and apoe genotype differences related to statin use in the aging population. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *7*, 7.

Dai, L., Zou, L., Meng, L., Qiang, G., Yan, M., & Zhang, Z. (2021). Cholesterol metabolism in neurodegenerative diseases: Molecular mechanisms and therapeutic targets. *Molecular Neurobiology*, *58*, 2183–2201.

Davis, E. J., Broestl, L., Abdulai-Saiku, S., Worden, K., Bonham, L. W., Miñones-Moyano, E., Moreno, A. J., Wang, D., Chang, K., Williams, G., Garay, B. I., Lobach, I., Devidze, N., Kim, D., Anderson-Bergman, C., Yu, G. Q., White, C. C., Harris, J. A., Miller, B. L., … Dubal, D. B. (2020). A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease. *Science Translational Medicine*, *12*(558), eaaz5677. https://doi.org/10.1126/scitranslmed.aaz5677

de Carvalho Guimarães, B., Valente Pereira, A. C., da Costa Rodrigues, F., Vaz dos Santos, A., Júnior, M. C., Mendonça dos Santos, J., Lima dos Santos, F., Zuma de Rosso, A. L., Nicaretta, D. H., Pereira, J. S., José da Silva, D., Della Coletta, M. V., Santos-Rebouças, C. B., & Gonçalves Pimentel, M. M. (2012). Glucocerebrosidase N370S and L444P mutations as risk factors for Parkinson's disease in Brazilian patients. *Parkinsonism & Related Disorders*, *18*(5), 688–689.

de Chaves, E. P., & Narayanaswami, V. (2008). Apolipoprotein E and cholesterol in aging and disease in the brain. *Future Lipidology*, *3*(5), 505–530.

de Rojas, I., Moreno-Grau, S., Tesi, N., Grenier-Boley, B., Andrade, V., Jansen, I. E., Pedersen, N. L., Stringa, N., Zettergren, A., Hernández, I., Montrreal, L., Antúnez, C., Antonell, A., Tankard, R. M., Bis, J. C., Sims, R., Bellenguez, C., Quintela, I., González-Perez, A., … Ruiz, A. (2021). Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. *Nature Communications*, *12*, 3417.

De Virgilio, A., Greco, A., Fabbrini, G., Inghilleri, M., Rizzo, M. I., Gallo, A., Conte, M., Rosato, C., Ciniglio, A. M., & de Vincentiis, M. (2016). Parkinson's disease: Autoimmunity and neuroinflammation. *Autoimmunity Reviews*, *15*(10), 1005–1011.

DeCasien, A. R., Guma, E., Liu, S., & Raznahan, A. (2022). Sex differences in the human brain: A roadmap for more careful analysis and interpretation of a biological reality. *Biology of Sex Differences*, *13*(1), 43.

den Hoedt, S., Crivelli, S. M., Leijten, F. P. J., Losen, M., Stevens, J. A. A., Mané-Damas, M., de Vries, H. E., Walter, J., Mirzaian, M., Sijbrands, E. J. G., Aerts, J. M. F. G., Verhoeven, A. J. M., Martinez-Martinez, P., & Mulder, M. T. (2021). Effects of sex, age, and apolipoprotein E genotype on brain ceramides and sphingosine-1-phosphate in Alzheimer's disease and control mice. *Frontiers in Aging Neuroscience*, *13*, 1–11.

Derby, C. A., Crawford, S. L., Pasternak, R. C., Sowers, M., Sternfeld, B., & Matthews, K. A. (2009). Lipid changes during the menopause transition in relation to age and weight. *American Journal of Epidemiology*, *169*, 1352–1361.

Di Domenico, F., Tramutola, A., & Butterfield, D. A. (2017). Role of 4-hydroxy-2-nonenal (HNE) in the pathogenesis of Alzheimer's disease and other selected age-related neurodegenerative disorders. *Free Radical Biology & Medicine*, *111*, 253–261.

Díaz, M., Fabelo, N., Ferrer, I., & Marín, R. (2018). "Lipid raft aging" in the human frontal cortex during nonpathological aging: Gender influences and potential implications in Alzheimer's disease. *Neurobiology of Aging*, *67*, 42–52.

Do, C. B., Tung, J. Y., Dorfman, E., Kiefer, A. K., Drabant, E. M., Francke, U., Mountain, J. L., Goldman, S. M., Tanner, C. M., Langston, J. W., Wojcicki, A., & Eriksson, N. (2011). Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. *PLoS Genetics*, *7*, 7.

Domingues, R. M., Domingues, P., Melo, T., Pérez-Sala, D., Reis, A., & Spickett, C. M. (2013). Lipoxidation adducts with peptides and proteins: Deleterious modifications or signaling mechanisms? *Journal of Proteomics*, *92*, 110–131.

Dong, H. K., Gim, J. A., Yeo, S. H., & Kim, H. S. (2017). Integrated late onset Alzheimer's disease (LOAD) susceptibility genes: Cholesterol metabolism and trafficking perspectives. *Gene*, *597*, 10–16.

Drouva, S. V., Rerat, E., Leblanc, P., Laplante, E., & Kordon, C. (1987). Variations of phospholipid methyltransferase(s) activity in the rat pituitary: Estrous cycle and sex differences. *Endocrinology*, *121*, 569–574.

Duarte-Guterman, P., Yagi, S., Chow, C., & Galea, L. A. M. (2015). Hippocampal learning, memory, and neurogenesis: Effects of sex and estrogens across the lifespan in adults. *Hormones and Behavior*, *74*, 37–52.

Dubal, D. B. (2020). Sex difference in Alzheimer's disease: An updated, balanced and emerging perspective on differing vulnerabilities. *Handbook of Clinical Neurology*, *175*, 261–273. https://doi.org/10.1016/B978-0-444-64123-6.00018-7

Duckles, S. P., & Krause, D. N. (2007). Cerebrovascular effects of oestrogen: Multiplicity of action. *Clinical and Experimental Pharmacology & Physiology*, *34*, 801–808.

Duka, T., Tasker, R., & McGowan, J. F. (2000). The effects of 3-week estrogen hormone replacement on cognition in elderly healthy females. *Psychopharmacology*, *149*, 129–139.

Egawa, J., Pearn, M. L., Lemkuil, B. P., Patel, P. M., & Head, B. P. (2016). Membrane lipid rafts and neurobiology: Age-related changes in membrane lipids and loss of neuronal function. *The Journal of Physiology*, *594*, 4565–4579.

Ekstrand, B., Scheers, N., Rasmussen, M. K., Young, J. F., Ross, A. B., & Landberg, R. (2021). Brain foods—The role of diet in brain performance and health. *Nutrition Reviews*, *79*(6), 693–708.

Fadeyibi, O., Rybalchenko, N., Mabry, S., Nguyen, D. H., & Cunningham, R. L. (2022). The role of lipid rafts and membrane androgen receptors in androgen's neurotoxic Effects. *Journal of the Endocrine Society*, *6*(5), bvac030. https://doi.org/10.1210/jendso/bvac030

Faubion, S. S., Kapoor, E., Moyer, A. M., Hodis, H. N., & Miller, V. M. (2019). Statin therapy: Does sex matter? *Menopause*, *26*(12), 1425–1435.

Ferdouse, A., Leng, S., Winter, T., & Aukema, H. M. (2019). The brain Oxylipin profile is resistant to modulation by dietary n-6 and n-3 polyunsaturated fatty acids in male and female rats. *Lipids*, *54*, 67–80.

Fernandez, H. H., & Lapane, K. L. (2002). Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. *Medical Science Monitor*, *8*, 241–247.

Ferretti, M. T., Martinkova, J., Biskup, E., Benke, T., Gialdini, G., Nedelska, Z., Rauen, K., Mantua, V., Religa, D., Hort, J., Santuccione Chadha, A., & Schmidt, R. (2020). Sex and gender differences in Alzheimer's disease: Current challenges and implications for clinical practice: Position paper of the dementia and cognitive disorders panel of the European academy of neurology. *European Journal of Neurology*, *27*, 928–943.

Forger, N. G. (2016). Epigenetic mechanisms in sexual differentiation of the brain and behaviour. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *371*(1688), 20150114.

Frieden, C., Wang, H., & Ho, C. M. W. (2017). A mechanism for lipid binding to apoE and the role of intrinsically disordered regions coupled to domain-domain interactions. *Proceedings of the National Academy of Sciences of the United States of America*, *114*, 6292–6297.

Fritsche, K. L. (2015). The science of fatty acids and inflammation. *Advances in nutrition (Bethesda, Md.)*, *6*(3), 293S–301S. https://doi.org/10.3945/an.114.006940

Fu, Y., He, Y., Phan, K., Pickford, R., Kim, Y. B., Dzamko, N., Halliday, G. M., & Kim, W. S. (2022). Sex-specific lipid dysregulation in the *Abca7* knockout mouse brain. *Brain Communications*, *4*(3), fcac120. https://doi.org/10.1093/braincomms/fcac120

Fu, Y., Hsiao, J. H. T., Paxinos, G., Halliday, G. M., & Kim, W. S. (2016). ABCA7 mediates phagocytic clearance of amyloid-β in the brain. *Journal of Alzheimer's Disease*, *54*, 569–584.

Gaamouch, F. E.l., Jing, P., Xia, J., & Cai, D. (2016). Alzheimer's disease risk genes and lipid regulators. *Journal of Alzheimer's Disease*, *53*(1), 15–29.

Gall, C. M., Le, A. A., & Lynch, G. (2023). Sex differences in synaptic plasticity underlying learning. *Journal of Neuroscience Research*, *101*(5), 764–782. https://doi.org/10.1002/jnr.24844

Galli, C., White, H. B., & Paoletti, R. (1970). Brain lipid modifications induced by essential fatty acid deficiency in growing male and female rats. *Journal of Neurochemistry*, *17*, 347–355.

Galper, J., Dean, N. J., Pickford, R., Lewis, S. J. G., Halliday, G. M., Kim, W. S., & Dzamko, N. (2022). Lipid pathway dysfunction is prevalent in patients with Parkinson's disease. *Brain*, *145*(10), 3472–3487.

Gamache, J., Yun, Y., & Chiba-Falek, O. (2020). Sex-dependent effect of APOE on Alzheimer's disease and other age-related neurodegenerative disorders. *Disease Models and Mechanisms*, *13*, 13.

Gan-Or, Z., Ozelius, L. J., Bar-Shira, A., Saunders-Pullman, R., Mirelman, A., Kornreich, R., Gana-Weisz, M., Raymond, D., Rozenkrantz, L., Deik, A., Gurevich, T., Gross, S. J., Schreiber-Agus, N., Giladi, N., Bressman, S. B., & Orr-Urtreger, A. (2013). The p.L302P mutation in the lysosomal enzyme gene SMPD1 is a risk factor for Parkinson disease. *Neurology*, *80*, 1606–1610.

Gao, Y., Tang, Y., Zhang, H., Yang, Y., Dong, T., & Jia, Q. (2022). Sex differences of cerebellum and cerebrum: Evidence from graph convolutional network. *Interdisciplinary Sciences: Computational Life Sciences*, *14*, 532–544.

Garza-Contreras, J., Duong, P., Snyder, B. D., Schreihofer, D. A., & Cunningham, R. L. (2017). Presence of androgen receptor variant in neuronal lipid rafts. *eNeuro*, *4*, ENEURO.0109–ENEU17.2017.

Gaudet, D., Drouin-Chartier, J. P., & Couture, P. (2017). Lipid metabolism and emerging targets for lipid-lowering therapy. *The Canadian Journal of Cardiology*, *33*, 872–882.

Gegenhuber, B., & Tollkuhn, J. (2020). Signatures of sex: Sex differences in gene expression in the vertebrate brain. *Wiley Interdisciplinary Reviews: Developmental Biology*, *9*, e348.

Gerges, S. H., & El-Kadi, A. O. S. (2022). Sexual dimorphism in the expression of cytochrome P450 enzymes in rat heart, liver, kidney, lung, brain, and Small intestine. *Drug Metabolism and Disposition*, *51*(1), 81–94.

Ghanem, A. C., Degerny, C., Hussain, R., Liere, P., Pianos, A., Tourpin, S., Habert, R., Macklin, W. B., Schumacher, M., & Ghoumari, A. M. (2017). Long-lasting masculinizing effects of postnatal androgens on myelin governed by the brain androgen receptor. *PLoS Genetics*, *13*, 13.

Gildawie, K. R., Orso, R., Peterzell, S., Thompson, V., & Brenhouse, H. C. (2020). Sex differences in prefrontal cortex microglia morphology: Impact of a two-hit model of adversity throughout development. *Neuroscience Letters*, *738*, 135381.

Gillett, M. J., Martins, R. N., Clarnette, R. M., Chubb, S. A. P., Bruce, D. G., & Yeap, B. B. (2003). Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. *Journal of Alzheimer's Disease*, *5*, 267–269.

Gillies, G. E., Pienaar, I. S., Vohra, S., & Qamhawi, Z. (2014). Sex differences in Parkinson's disease. *Frontiers in Neuroendocrinology*, *35*, 370–384.

Ginder, D. E., Wright, H. R., & McLaughlin, R. J. (2022). The stoned age: Sex differences in the effects of adolescent cannabinoid exposure on prefrontal cortex structure and function in animal models. *International Review of Neurobiology*, *161*, 121–145. https://doi.org/10.1016/bs.irn.2021.07.005

Goldstein, J. M., Seidman, L. J., Horton, N. J., Makris, N., Kennedy, D. N., Caviness, V. S., Faraone, S. V., & Tsuang, M. T. (2001). Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex*, *11*, 11–497.

Gorski, R. A., Gordon, J. H., Shryne, J. E., & Southam, A. M. (1978). Evidence for a morphological sex difference within the medial preoptic area of the rat brain. *Brain Research*, *148*, 333–346.

Grassi, S., Giussani, P., Mauri, L., Prioni, S., Sonnino, S., & Prinetti, A. (2020). Lipid rafts and neurodegeneration: Structural and functional roles in physiologic aging and neurodegenerative diseases. *Journal of Lipid Research*, *61*, 636–654.

Growdon, J. H., & Hyman, B. T. (2014). APOE genotype and brain development. *JAMA Neurology*, *71*(1), 7–8.

Guillamón, A., Segovia, S., Abril, A., & del. (1988). Early effects of gonadal steroids on the neuron number in the medial posterior region and the lateral division of the bed nucleus of the stria terminalis in the rat. *Developmental Brain Research*, *44*, 44–290.

Guo, X., Qiu, W., Garcia-Milian, R., Lin, X., Zhang, Y., Cao, Y., Tan, Y., Wang, Z., Shi, J., Wang, J., Liu, D., Song, L., Xu, Y., Wang, X., Liu, N., Sun, T., Zheng, J., Luo, J., Zhang, H., … Luo, X. (2017). Genome-wide significant, replicated and functional risk variants for Alzheimer's disease. *Journal of Neural Transmission (Vienna, Austria:1996)*, *124*(11), 1455–1471. https://doi.org/10.1007/s00702-017-1773-0

Gurvich, C., Thomas, N., & Kulkarni, J. (2020). Sex differences in cognition and aging and the influence of sex hormones. *Handbook of Clinical Neurology*, *175*, 103–115.

Haaxma, C. A., Bloem, B. R., Borm, G. F., Oyen, W. J. G., Leenders, K. L., Eshuis, S., Booij, J., Dluzen, D. E., & Horstink, M. W. I. M. (2007). Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *78*, 819–824.

Hadaczek, P., Wu, G., Sharma, N., Ciesielska, A., Bankiewicz, K., Davidow, A. L., Lu, Z. H., Forsayeth, J., & Ledeen, R. W. (2015). GDNF signaling implemented by GM1 ganglioside; failure in Parkinson's disease and GM1-deficient murine model. *Experimental Neurology*, *263*, 177–189.

Hallett, P. J., Engelender, S., & Isacson, O. (2019). Lipid and immune abnormalities causing age-dependent neurodegeneration and Parkinson's disease. *Journal of Neuroinflammation*, *16*, 1–15.

Hansberg-Pastor, V., González-Arenas, A., Piña-Medina, A. G., & Camacho-Arroyo, I. (2015). Sex hormones regulate cytoskeletal proteins involved in brain plasticity. *Frontiers in Psychiatry*, *6*, 165.

Hanukoglu, I., Karavolas, H. J., & Goy, R. W. (1977). Progesterone metabolism in the pineal, brain stem, thalamus and corpus callosum of the female rat. *Brain Research*, *125*, 313–324.

Hao, J., Rapp, P. R., Janssen, W. G. M., Lou, W., Lasley, B. L., Hof, P. R., & Morrison, J. H. (2007). Interactive effects of age and estrogen on cognition and pyramidal neurons in monkey prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 11465–11470.

Hartmann, P. A. (2011). Going the wrong road: Fyn and targeting of amyloid precursor protein to lipid rafts. *Journal of Neurochemistry*, *118*, 677–679.

Heck, A. L., & Handa, R. J. (2019). Sex differences in the hypothalamic–pituitary–adrenal axis' response to stress: An important role for gonadal hormones. *Neuropsychopharmacology*, *44*(1), 45–58.

Henderson, V. W., & Buckwalter, J. G. (1994). Cognitive deficits of men and women with alzheimer's disease. *Neurology*, *44*, 90.

Hennebelle, M., Morgan, R. K., Sethi, S., Zhang, Z., Chen, H., Grodzki, A. C., Lein, P. J., & Taha, A. Y. (2020). Linoleic acid-derived metabolites constitute the majority of oxylipins in the rat pup brain and stimulate axonal growth in primary rat cortical neuron-glia co-cultures in a sex-dependent manner. *Journal of Neurochemistry*, *152*, 195–207.

Hillard, C. J. (2018). Circulating endocannabinoids: From whence Do they come and where are they Going? *Neuropsychopharmacology*, *43*(1), 155–172.

Hohman, T. J., Dumitrescu, L., Barnes, L. L., Thambisetty, M., Beecham, G., Kunkle, B., Gifford, K. A., Bush, W. S., Chibnik, L. B., Mukherjee, S., de Jager, P. L., Kukull, W., Crane, P. K., Resnick, S. M., Keene, C. D., Montine, T. J., Schellenberg, G. D., Haines, J. L., Zetterberg, H., … for the Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative. (2018). Sex-specific association of apolipoprotein e with cerebrospinal fluid levels of tau. *JAMA Neurology*, *75*, 989–998.

Hojo Y., Higo S., Ishii,H., Ooishi Y., Mukai H., Murakami G., Kominami T., Kimoto T., Honma S., Poirier D., Kawato S. (2009) Comparison between hippocampus- synthesized and circulation-derived sex steroids in the hippocampus. *Endocrinology 150* (11), 5106–5112.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., Abraham, R., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone, S., … Williams, J. (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature Genetics*, *43*, 429–436.

Hong, D. S., & Reiss, A. L. (2014). Cognitive and neurological aspects of sex chromosome aneuploidies. *Lancet Neurology*, *13*(3), 306–318.

Hsue, P. Y., Bittner, V. A., Betteridge, J., Fayyad, R., Laskey, R., Wenger, N. K., & Waters, D. D. (2015). Impact of female sex on lipid lowering, clinical outcomes, and adverse effects in atorvastatin trials. *The American Journal of Cardiology*, *115*, 447–453.

Huang, G. Z., & Woolley, C. S. (2012). Estradiol acutely suppresses inhibition in the hippocampus through a sex-specific endocannabinoid and mGluR-dependent mechanism. *Neuron*, *74*, 801–808.

Iliff, J. J., Jia, J., Nelson, J., Goyagi, T., Klaus, J., & Alkayed, N. J. (2010). Epoxyeicosanoid signaling in CNS function and disease. *Prostaglandins & Other Lipid Mediators*, *91*(3–4), 68–84.

Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T. D., Elliott, M. A., Ruparel, K., Hakonarson, H., Gur, R. E., Gur, R. C., & Verma, R. (2014). Sex differences in the structural connectome of the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 823–828.

Itokazu, Y., Wang, J., & Yu, R. K. (2018). Gangliosides in nerve cell specification. *Progress in Molecular Biology and Translational Science*, *156*, 241–263. https://doi.org/10.1016/bs.pmbts.2017.12.008

Izco, M., Carlos, E., & Alvarez-Erviti, L. (2022). Impact of endolysosomal dysfunction upon exosomes in neurodegenerative diseases. *Neurobiology of Disease*, *166*, 105651.

Jacenik, D., Bagüés, A., López-Gómez, L., López-Tofiño, Y., Iriondo-DeHond, A., Serra, C., Banovcanová, L., Gálvez-Robleño, C., Fichna, J., Del Castillo, M. D., Uranga, J. A., & Abalo, R. (2021). Changes in fatty acid dietary profile affect the brain-gut axis functions of healthy young adult rats in a sex-dependent manner. *Nutrients*, *13*(6), 1864. https://doi.org/10.3390/nu13061864

Janssen, C. I., & Kiliaan, A. J. (2014). Long-chain polyunsaturated fatty acids (LCPUFA) from genesis to senescence: The influence of LCPUFA on neural development, aging, and neurodegeneration. *Progress in Lipid Research*, *53*, 1–17. https://doi.org/10.1016/j.plipres.2013.10.002

Jeong, S. H., Lee, H. S., Chung, S. J., Yoo, H. S., Jung, J. H., Baik, K., Lee, Y. H., Sohn, Y. H., & Lee, P. H. (2021). Effects of statins on dopamine loss and prognosis in Parkinson's disease. *Brain*, *144*, 3191–3200.

Jones, L., Holmans, P. A., Hamshere, M. L., Harold, D., Moskvina, V., Ivanov, D., Pocklington, A., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Pahwa, J. S., Jones, N., Stretton, A., Morgan, A. R., Lovestone, S., Powell, J., Proitsi, P., Lupton, M. K., … Williams, J. (2010). Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PloS One*, *5*(11), e13950. https://doi.org/10.1371/journal.pone.0013950

Jové, M., Pradas, I., Dominguez-Gonzalez, M., Ferrer, I., & Pamplona, R. (2019). Lipids and lipoxidation in human brain aging. Mitochondrial ATP-synthase as a key lipoxidation target. *Redox Biology*, *23*, 101082.

Kaczkurkin, A. N., Raznahan, A., & Satterthwaite, T. D. (2019). Sex differences in the developing brain: Insights from multimodal neuroimaging. *Neuropsychopharmacology*, *44*, 71–85.

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *Lancet*, *386*, 896–912.

Kao, Y., Ho, P., Tu, Y., Jou, I., & Tsai, K. (2020). Lipids and Alzheimer ' s disease. *International Journal of Molecular Sciences*, *21*, 1505.

Karimi, R., Zarepur, E., Khosravi, A., Mohammadifard, N., Nouhi, F., Alikhasi, H., Nasirian, S., Sadeghi, M., Roohafza, H., Moezi Bady, S. A., Janjani, P., Solati, K., Lotfizadeh, M., Ghaffari, S., Javanmardi, E., Gholipour, M., Dehghani, M., Cheraghi, M., Assareh, A., … Sarrafzadegan, N. (2023). Ethnicity based differences in statin use and hypercholesterolemia control among patients with premature coronary artery disease-results of I-PAD study. *International Journal of Cardiology Cardiovascular Risk and Prevention*, *16*, 200168.

Kay, J. G., & Grinstein, S. (2013). Phosphatidylserine-mediated cellular signaling. *Advances in Experimental Medicine and Biology*, *991*, 177–193. https://doi.org/10.1007/978-94-007-6331-9_10

Khan, S. U., Khan, M. Z., Raghu Subramanian, C., Riaz, H., Khan, M. U., Lone, A. N., Khan, M. S., Benson, E. M., Alkhouli, M., Blaha, M. J., Blumenthal, R. S., Gulati, M., & Michos, E. D. (2020). Participation of women and older participants in randomized clinical trials of lipid-lowering therapies: A systematic review. *JAMA Network Open*, *3*(5), e205202.

Kiely, K. M., Brady, B., & Byles, J. (2019). Gender, mental health and ageing. *Maturitas*, *129*, 76–84.

Kight, K. E., McCarthy, M. M., & McCarthy, M. M. (2020). Androgens and the developing hippocampus. *Biology of Sex Differences*, *11*(1), 30.

Kim, R., Park, S., Yoo, D., Ju, S. Y., Jun, J. S., & Jeon, B. (2021). Potential sex-specific effects of apolipoprotein e ϵ4 on cognitive decline in early Parkinson's disease. *Journal of Parkinson's Disease*, *11*, 497–505.

Kim, W. S., Fitzgerald, M. L., Kang, K., Okuhira, K. I., Bell, S. A., Manning, J. J., Koehn, S. L., Lu, N., Moore, K. J., & Freeman, M. W. (2005). Abca7 null mice retain normal macrophage phosphatidylcholine and cholesterol efflux activity despite alterations in adipose mass and serum cholesterol levels. *The Journal of Biological Chemistry*, *280*, 41953–41966.

Kissoondoyal, A., Rai-Bhogal, R., & Crawford, D. A. (2021). Abnormal dendritic morphology in the cerebellum of cyclooxygenase-2–knockin mice. *The European Journal of Neuroscience*, *54*, 6355–6373.

Kitson, A. P., Smith, T. L., Marks, K. A., & Stark, K. D. (2012). Tissue-specific sex differences in docosahexaenoic acid and Δ6-desaturase in rats fed a standard chow diet. *Applied Physiology, Nutrition, and Metabolism*, *37*, 1200–1211.

Kloske, C. M., & Wilcock, D. M. (2020). The important Interface between Apolipoprotein E and Neuroinflammation in Alzheimer's disease. *Frontiers in Immunology*, *11*, 754.

Kochmanski, J., Kuhn, N. C., & Bernstein, A. I. (2022). Parkinson's disease-associated, sex-specific changes in DNA methylation at PARK7 (DJ-1), SLC17A6 (VGLUT2), PTPRN2 (IA-2β), and NR4A2 (NURR1) in cortical neurons. *NPJ Parkinson's Disease*, *8*(1), 120.

Kogot-Levin, A., & Saada, A. (2014). Ceramide and the mitochondrial respiratory chain. *Biochimie*, *100*, 88–94. https://doi.org/10.1016/j.biochi.2013.07.027

Kolata, G. B. (1979). Sex hormones and brain development. *Science*, *205*(4410), 985–987.

Koran, M. E. I., Wagener, M., & Hohman, T. J. (2017). Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging and Behavior*, *11*, 205–213.

Kosowski, M., Smolarczyk-Kosowska, J., Hachuła, M., Maligłówka, M., Basiak, M., Machnik, G., Pudlo, R., & Okopień, B. (2021). The effects of statins on neurotransmission and their neuroprotective role in neurological and psychiatric disorders. *Molecules*, *26*, 1–19.

Kracun, I., Kalanj, S., Talan-Hranilovic, J., & Cosovic, C. (1992). Cortical distribution of gangliosides in Alzheimer's disease. *Neurochemistry International*, *20*, 433–438.

Krishnaswami, A., Beavers, C., Dorsch, M. P., Dodson, J. A., Masterson Creber, R., Kitsiou, S., Goyal, P., Maurer, M. S., Wenger, N. K., Croy, D. S., Alexander, K. P., Batsis, J. A., Turakhia, M. P., Forman, D. E., Bernacki, G. M., Kirkpatrick, J. N., Orr, N. M., Peterson, E. D., Rich, M. W., … Bhavnani, S. P. (2020). Gerotechnology for older adults with cardiovascular diseases: JACC state-of-the-art review. *Journal of the American College of Cardiology*, *76*, 2650–2670.Innovations, Cardiovascular Team and the Geriatric Cardiology Councils, American College of Cardiology

Kritzer, M. F., & Creutz, L. M. (2008). Region and sex differences in constituent dopamine neurons and immunoreactivity for intracellular estrogen and androgen receptors in mesocortical projections in rats. *The Journal of Neuroscience*, *28*, 9525–9535.

Kuang, Z. M. (2020). Effect of combined antihypertensive and lipid-lowering therapies on cognitive function: A new treatment strategy? *Cardiology Research and Practice*, *2020*, 1–10.

Kunkle, B. W., Grenier-Boley, B., Sims, R., Bis, J. C., Damotte, V., Naj, A. C., Boland, A., Vronskaya, M., van der Lee, S. J., Amlie-Wolf, A., Bellenguez, C., Frizatti, A., Chouraki, V., Martin, E. R., Sleegers, K., Badarinarayan, N., Jakobsdottir, J., Hamilton-Nelson, K. L., Moreno-Grau, S., … Pericak-Vance, M. A. (2019). Author Correction: Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and

lipid processing. *Nature Genetics*, *51*(3), 414–430. https://doi.org/10.1038/s41588-019-0358-2

Kurz, E. M., Sengelaub, D. R., & Arnold, A. P. (1986). Androgens regulate the dendritic length of mammalian motoneurons in adulthood. *Science*, *232*(4748), 395–398.

La Rosa, P., Bartoli, G., Farioli Vecchioli, S., Cesari, E., Pagliarini, V., & Sette, C. (2021). Androgen Receptor signaling promotes the neural progenitor cell pool in the developing cortex. *Journal of Neurochemistry*, *157*(4), 1153–1166. https://doi.org/10.1111/jnc.15192

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., DeStafano, A. L., Bis, J. C., Beecham, G. W., Grenier-Boley, B., Russo, G., Thorton-Wells, T. A., Jones, N., Smith, A. V., Chouraki, V., Thomas, C., Ikram, M. A., Zelenika, D., Vardarajan, B. N., … Amouyel, P. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*, *45*, 1452–1458.

Larson, T. A. (2018). Sex steroids, adult neurogenesis, and inflammation in CNS homeostasis, degeneration, and repair. *Frontiers in Endocrinology*, *9*, 205. https://doi.org/10.3389/fendo.2018.00205

Lauwers, E., Goodchild, R., & Verstreken, P. (2016). Membrane lipids in presynaptic function and disease. *Neuron*, *90*, 11–25.

Ledesma, M. D., Martin, M. G., & Dotti, C. G. (2012). Lipid changes in the aged brain: Effect on synaptic function and neuronal survival. *Progress in Lipid Research*, *51*, 23–35.

Leranth, C., Hajszan, T., & MacLusky, N. J. (2004). Androgens increase spine synapse density in the CA1 hippocampal subfield of Ovariectomized female rats. *The Journal of Neuroscience*, *24*, 495–499.

Leranth, C., Petnehazy, O., & MacLusky, N. J. (2003). Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. *The Journal of Neuroscience*, *23*, 1588–1592.

Levant, B., Ozias, M. K., & Carlson, S. E. (2006). Sex-specific effects of brain LC-PUFA composition on locomotor activity in rats. *Physiology & Behavior*, *89*, 196–204.

Lewis, C., McEwen, B. S., & Frankfurt, M. (1995). Estrogen-induction of dendritic spines in ventromedial hypothalamus and hippocampus: Effects of neonatal aromatase blockade and adult GDX. *Developmental Brain Research*, *87*, 91–95.

Li, X., Kan, H. Y., Lavrentiadou, S., Krieger, M., & Zannis, V. (2002). Reconstituted discoidal apoE-phospholipid particles are ligands for the scavenger receptor BI. The amino-terminal 1-165 domain of apoE suffices for receptor binding. *The Journal of Biological Chemistry*, *277*, 50607–50611.

Li, Y., Zhao, T., Li, J., Xia, M., Li, Y., Wang, X., Liu, C., Zheng, T., Chen, R., Kan, D., Xie, Y., Song, J., Feng, Y., Yu, T., & Sun, P. (2022). Oxidative stress and 4-hydroxy-2-nonenal (4-HNE): Implications in the pathogenesis and treatment of aging-related diseases. *Journal of Immunology Research*, *2022*, 1–12.

Lingwood, D., & Simons, K. (2010). Lipid rafts as a membrane-organizing principle.

Logge, W., Cheng, D., Chesworth, R., Bhatia, S., Garner, B., Kim, W. S., & Karl, T. (2012). Role of Abca7 in mouse Behaviours relevant to neurodegenerative diseases. *PLoS One*, *7*, e45959.

Luque, J. M., Blas, M. R., de Segovia, S., & Guillamón, A. (1992). Sexual dimorphism of the dopamine-β-hydroxylase-immunoreactive neurons in the rat locus ceruleus. *Developmental Brain Research*, *67*, 211–215.

Ma, X., Li, X., Wang, W., Zhang, M., Yang, B., & Miao, Z. (2022). Phosphatidylserine, inflammation, and central nervous system diseases. *Frontiers in Aging Neuroscience*, *14*, 1–18.

Ma, Y. Y., Kong, S. Z., Yang, L. J., Meng, J. L., Lv, L. C., & He, M. (2007). Sexual dimorphisms of dopaminergic neurons in rat substantia nigra. *Sheng Li Xue Bao*, *59*, 753–758.

MacLusky, N. J., Hajszan, T., Johansen, J. A., Jordan, C. L., & Leranth, C. (2006). Androgen effects on hippocampal CA1 spine synapse numbers are retained in Tfm male rats with defective androgen receptors. *Endocrinology*, *147*, 2392–2398.

Madeira, M. D., & Paula-Barbosa, M. M. (1993). Reorganization of mossy fiber synapses in male and female hypothyroid rats: A stereological study. *The Journal of Comparative Neurology*, *337*, 334–352.

Madeira, M. D., Sousa, N., & Paula-Barbosa, M. M. (1991). Sexual dimorphism in the mossy fiber synapses of the rat hippocampus. *Experimental Brain Research*, *87*, 537–545.

Maioli, S., Leander, K., Nilsson, P., & Nalvarte, I. (2021). Estrogen receptors and the aging brain. *Essays in Biochemistry*, *65*(6), 913–925.

Marin, R., Casañas, V., Pérez, J. A., Fabelo, N., Fernandez, C. E., & Diaz, M. (2013). Oestrogens as modulators of neuronal signalosomes and brain lipid homeostasis related to protection against neurodegeneration. *Journal of Neuroendocrinology*, *25*(11), 1104–1115.

Marin, R., & Diaz, M. (2018). Estrogen interactions with lipid rafts related to neuroprotection. Impact of brain ageing and menopause. *Frontiers in Neuroscience*, *12*, 128.

Martin, R., & Sospedra, M. (2014). Sphingosine-1 phosphate and central nervous system. *Current topics in Microbiology and Immunology*, *378*, 149–170. https://doi.org/10.1007/978-3-319-05879-5_7

Martinsen, A., Tejera, N., Vauzour, D., Harden, G., Dick, J., Shinde, S., Barden, A., Mori, T. A., & Minihane, A. M. (2019). Altered SPMs and age-associated decrease in brain DHA in APOE4 female mice. *The FASEB Journal*, *33*, 10315–10326.

Maselli, A., Pierdominici, M., Vitale, C., & Ortona, E. (2015). Membrane lipid rafts and estrogenic signalling: A functional role in the modulation of cell homeostasis. *Apoptosis*, *20*(5), 671–678.

Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. *Nature Reviews Disease Primers*, *1*, 1–18.

Mata, I. F., Samii, A., Schneer, S. H., Roberts, J. W., Griffith, A., Leis, B. C., Schellenberg, G. D., Sidransky, E., Bird, T. D., Leverenz, J. B., Tsuang, D., & Zabetian, C. P. (2008). Glucocerebrosidase gene mutations: A risk factor for Lewy body disorders. *Archives of Neurology*, *65*, 379–382.

Mathias, J. R., Dodd, M. E., Walters, K. B., Yoo, S. K., Erik, A., & Huttenlocher, A. (2010). Modeling a sensitization stage and a precipitation stage for Parkinson's disease using prenatal and postnatal 1-Methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. *Neuroscience*, *169*(3), 1085–1093.

Matsumoto, A., & Arai, Y. (1983). Sex difference in volume of the ventromedial nucleus of the hypothalamus in the rat. *Endocrinologia Japonica*, *30*(3), 277–280.

Mauvais-Jarvis, F., Bairey, M. N., Barnes, P. J., Brinton, R. D., Carrero, J. J., DeMeo, D. L., De Vries, G. J., et al. (2020). Sex and gender: Modifiers of health, disease, and medicine. *Lancet*, *396*(10250), 565–582.

McCarthy, M. M. (2020). A new view of sexual differentiation of mammalian brain. *Journal of Comparative Physiology. A, Neuroethology, Sensory, Neural, and Behavioral Physiology*, *206*(3), 369–378.

McCarthy, M. M., Auger, A. P., & Perrot-Sinal, T. S. (2002). Getting excited about GABA and sex differences in the brain. *Trends in Neurosciences*, *25*, 307–312.

McEwen, B. S., & Milner, T. A. (2017). Understanding the broad influence of sex hormones and sex differences in the brain. *Journal of Neuroscience Research*, *95*, 24–39.

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: Hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*, *41*(1), 3–23.

McFarlane, O., & Kędziora-Kornatowska, K. (2019). Cholesterol and dementia: A long and complicated relationship. *Current Aging Science*, *13*, 42–51.

McGrattan, A. M., McGuinness, B., McKinley, M. C., Kee, F., Passmore, P., Woodside, J. V., & McEvoy, C. T. (2019). Diet and inflammation in cognitive ageing and Alzheimer's disease. *Current Nutrition Reports*, *8*, 53–65.

McNamara, R. K., Liu, Y., Jandacek, R., Rider, T., & Tso, P. (2008). The aging human orbitofrontal cortex: Decreasing polyunsaturated fatty acid composition and associated increases in lipogenic gene expression and stearoyl-CoA desaturase activity. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *78*(4–5), 293–304.

Mena, E., & Bolte, G. (2019). Intersectionality-based quantitative health research and sex/gender sensitivity: A scoping review. *International Journal for Equity in Health*, *18*(1), 199.

Mencarelli, C., & Martinez-Martinez, P. (2013). Ceramide function in the brain: When a slight tilt is enough. *Cellular and Molecular Life Sciences : CMLS*, *70*(2), 181–203. https://doi.org/10.1007/s00018-012-1038-x

Mercuro, G., Deidda, M., Bina, A., Manconi, E., & Rosano, G. M. (2011). Gender-specific aspects in primary and secondary prevention of cardiovascular disease. *Current Pharmaceutical Design*, *17*(11), 1082–1089. https://doi.org/10.2174/138161211795656954

Mesa-Herrera, F., Taoro-González, L., Valdés-Baizabal, C., Diaz, M., & Marín, R. (2019). Lipid and lipid raft alteration in aging and neurodegenerative diseases: A window for the development of new biomarkers. *International Journal of Molecular Sciences*, *20*(15), 3810. https://doi.org/10.3390/ijms20153810

Mielke, M. M., Ferretti, M. T., Iulita, M. F., Hayden, K., & Khachaturian, A. S. (2018). Sex and gender in Alzheimer's disease—Does it matter? *Alzheimer's Dement*, *14*, 1101–1103.

Mielke, M. M., Vemuri, P., & Rocca, W. A. (2014). Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. *Clinical Epidemiology*, *6*, 37–48.

Moffat, S. D., Zonderman, A. B., Metter, E. J., Kawas, C., Blackman, M. R., Harman, S. M., & Resnick, S. M. (2004). Free testosterone and risk for Alzheimer disease in older men. *Neurology*, *62*, 188–193.

Moll, T., Marshall, J. N. G., Soni, N., Zhang, S., Cooper-Knock, J., & Shaw, P. J. (2021). Membrane lipid raft homeostasis is directly linked to neurodegeneration. *Essays in Biochemistry*, *65*, 999–1011.

Moll, T., Shaw, P. J., & Cooper-Knock, J. (2020). Disrupted glycosylation of lipids and proteins is a cause of neurodegeneration. *Brain*, *143*, 143–1340.

Moor, E., Shohami, E., Kanevsky, E., Grigoriadis, N., Symeonidou, C., & Kohen, R. (2006). Impairment of the ability of the injured aged brain in elevating urate and ascorbate. *Experimental Gerontology*, *41*, 303–311.

Morselli, E., de Souza Santos, R., Gao, S., Ávalos, Y., Criollo, A., Palmer, B. F., & Clegg, D. J. (2018). Impact of estrogens and estrogen receptor-α in brain lipid metabolism. *American Journal of Physiology-Endocrinology and Metabolism*, *315*, E7–E14.

Morselli, E., Frank, A. P., Palmer, B. F., Rodriguez-Navas, C., Criollo, A., & Clegg, D. J. (2016). A sexually dimorphic hypothalamic response to chronic high-fat diet consumption. *International Journal of Obesity*, *40*, 206–209.

Morselli, E., Fuente-Martin, E., Finan, B., Kim, M., Frank, A., Garcia-Caceres, C., Navas, C. R., Gordillo, R., Neinast, M., Kalainayakan, S. P., Li, D. L., Gao, Y., Yi, C. X., Hahner, L., Palmer, B. F., Tschöp, M. H., & Clegg, D. J. (2014). Hypothalamic PGC-1α protects against high-fat diet exposure by regulating ERα. *Cell Reports*, *9*, 633–645.

Mortensen, E. L., & Høgh, P. (2001). A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology*, *57*, 57–95.

Mukai, H., Tsurugizawa, T., Murakami, G., Kominami, S., Ishii, H., Ogiue-Ikeda, M., Takata, N., Tanabe, N., Furukawa, A., Hojo, Y., Ooishi, Y., Morrison, J. H., Janssen, W. G. M., Rose, J. A., Chambon, P., Kato, S., Izumi, S., Yamazaki, T., Kimoto, T., & Kawato, S. (2007). Rapid modulation of long-term depression and spinogenesis via synaptic estrogen receptors in hippocampal principal neurons. *Journal of Neurochemistry*, *100*, 950–967.

Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D., Tan, M., Kia, D. A., Noyce, A. J., Xue, A., Bras, J., Young, E., von Coelln, R., Simón-Sánchez, J., Schulte, C., Sharma, M., Krohn, L., Pihlstrøm, L., Siitonen, A., … Zhang, F. (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: A meta-analysis of genome-wide association studies. *Lancet Neurology*, *18*, 1091–1102.

Nanna, M. G., Navar, A. M., Wang, T. Y., Mi, X., Virani, S. S., Louie, M. J., Lee, L. V., Goldberg, A. C., Roger, V. L., Robinson, J., & Peterson, E. D. (2018). Statin use and adverse effects among adults >75 years of age: Insights from the patient and provider assessment of lipid management (PALM) registry. *Journal of the American Heart Association*, *7*(10), e008546. https://doi.org/10.1161/JAHA.118.008546

Nathan, B. P., Barsukova, A. G., Shen, F., McAsey, M., & Struble, R. G. (2004). Estrogen facilitates neurite extension via apolipoprotein E in cultured adult mouse cortical neurons. *Endocrinology*, *145*(7), 3065–3073.

Naudí, A., Cabré, R., Jové, M., Ayala, V., Gonzalo, H., Portero-Otín, M., Ferrer, I., & Pamplona, R. (2015). Lipidomics of human brain aging and Alzheimer's disease pathology. *International Review of Neurobiology*, *122*, 133–189.

Nebel, R. A., Aggarwal, N. T., Barnes, L. L., Gallagher, A., Goldstein, J. M., Kantarci, K., Mallampalli, M. P., Mormino, E. C., Scott, L., Yu, W. H., Maki, P. M., & Mielke, M. M. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's Dement*, *14*, 1171–1183.

Nelson, D. L., & Cox, M. M. (2017). *Lehninger principles of biochemistry* (7th ed.). W.H. Freeman.

Nettiksimmons, J., Tranah, G., Evans, D. S., Yokoyama, J. S., & Yaffe, K. (2016). Gene-based aggregate SNP associations between candidate AD genes and cognitive decline. *Age (Omaha)*, *38*, 38.

Neumann, J., Bras, J., Deas, E., O'Sullivan, S. S., Parkkinen, L., Lachmann, R. H., Li, A., Holton, J., Guerreiro, R., Paudel, R., Segarane, B., Singleton, A., Lees, A., Hardy, J., Houlden, H., Revesz, T., & Wood, N. W. (2009). Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain*, *132*, 1783–1794.

Nguyen, D., Dhanasekaran, P., Nickel, M., Mizuguchi, C., Watanabe, M., Saito, H., Phillips, M. C., & Lund-Katz, S. (2014). Influence of domain stability on the properties of human apolipoprotein E3 and E4 and mouse apolipoprotein e. *Biochemistry*, *53*, 4025–4033.

Nilsen, J., & Brinton, R. D. (2002). Impact of progestins on estrogen-induced neuroprotection: Synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. *Endocrinology*, *143*, 205–212.

Norman, J. E., Nuthikattu, S., Milenkovic, D., Rutledge, J. C., & Villablanca, A. C. (2022). Prostaglandins, leukotrienes and essential fatty acids A high sucrose diet modifies brain oxylipins in a sex-dependent manner. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *186*, 102506.

Obeso, J. A., Stamelou, M., Goetz, C. G., Poewe, W., Lang, A. E., Weintraub, D., Burn, D., Halliday, G. M., Bezard, E., Przedborski, S., Lehericy, S., Brooks, D. J., Rothwell, J. C., Hallett, M., DeLong, M. R., Marras, C., Tanner, C. M., Ross, G. W., Langston, J. W., … Stoessl, A. J. (2017). Past, present, and future of Parkinson's disease: A special essay on the 200th anniversary of the shaking palsy. *Movement Disorders*, *32*, 1264–1310.

O'Brien, J. S., & Sampson, E. L. (1965). Lipid composition of the normal human brain: Gray matter, white matter, and myelin. *Journal of Lipid Research*, *6*, 545–551.

Oguro, H., Okada, K., Yamaguchi, S., & Kobayashi, S. (1998). Sex differences in morphology of the brain stem and cerebellum with normal ageing. *Neuroradiology*, *40*, 788–792.

Ohsawa, T., & Shumiya, S. (1991). Age-related alteration of brain gangliosides in senescence-accelerated mouse (SAM)-P/8 9. *Mechanisms of Ageing and Development*, *59*, 263–274.

Olmastroni, E., Boccalari, M. T., Tragni, E., Rea, F., Merlino, L., Corrao, G., Catapano, A. L., & Casula, M. (2020). Sex-differences in factors and

outcomes associated with adherence to statin therapy in primary care: Need for customisation strategies. *Pharmacological Research*, *155*, 104514.

Olmos, G., Naftolin, F., Perez, J., Tranque, P. A., & Garcia-Segura, L. M. (1989). Synaptic remodeling in the rat arcuate nucleus during the estrous cycle. *Neuroscience*, *32*, 663–667.

Ooi, K. L. M., Vacy, K., & Boon, W. C. (2021). Fatty acids and beyond: Age and Alzheimer's disease related changes in lipids reveal the neuro-nutraceutical potential of lipids in cognition. *Neurochemistry International*, *149*, 105143.

Ortega, R. A., Bressman, S. B., Raymond, D., Ozelius, L. J., Katsnelson, V., Leaver, K., Swan, M. C., Shanker, V., Miravite, J., Wang, C., Bennett, S., & Saunders-Pullman, R. (2022). Differences in sex-specific frequency of Glucocerebrosidase variant carriers and familial parkinsonism. *Movement Disorders*, *37*(11), 2217–2225.

Ostermann, A. I., Reutzel, M., Hartung, N., Franke, N., Kutzner, L., Schoenfeld, K., Weylandt, K. H., Eckert, G. P., & Schebb, N. H. (2017). A diet rich in omega-3 fatty acids enhances expression of soluble epoxide hydrolase in murine brain. *Prostaglandins & Other Lipid Mediators*, *133*, 79–87.

Palestini, P., Toppi, N., Ferraretto, A., Pitto, M., & Masserini, M. (1997). Ganglioside lateralization in the brain of female rats. *Journal of Neuroscience Research*, *50*, 643–648.

Panzica, G. C., & Melcangi, R. C. (2016). Structural and molecular brain sexual differences: A tool to understand sex differences in health and disease. *Neuroscience and Biobehavioral Reviews*, *67*, 2–8.

Paoletti, A. M., Congia, S., Lello, S., Tedde, D., Orrù, M., Pistis, M., Pilloni, M., Zedda, P., Loddo, A., & Melis, G. B. (2004). Low androgenization index in elderly women and elderly men with Alzheimer's disease. *Neurology*, *62*, 301–303.

Paquette, M., Faubert, S., Saint-Pierre, N., Baass, A., & Bernard, S. (2023). Sex differences in LDL-C response to PCSK9 inhibitors: A real world experience. *Journal of Clinical Lipidology*, *17*(1), 142–149.

Parducz, A., & Garcia-Segura, L. M. (1993). Sexual differences in the synaptic connectivity in the rat dentate gyrus. *Neuroscience Letters*, *161*, 53–56.

Pasha, R., Azmi, S., Ferdousi, M., Kalteniece, A., Bashir, B., Gouni-Berthold, I., Malik, R. A., & Soran, H. (2022). Lipids, lipid-lowering therapy, and neuropathy: A narrative review. *Clinical Therapeutics*, *44*, 1012–1025.

Patisaul, H. B., Fortino, A. E., & Polston, E. K. (2008). Sex differences in serotonergic but not γ-aminobutyric acidergic (GABA) projections to the rat ventromedial nucleus of the hypothalamus. *Endocrinology*, *149*, 397–408.

Payami, H., Zareparsi, S., Montee, K. R., Sexton, G. J., Kaye, J. A., Bird, T. D., Yu, C. E., Wijsman, E. M., Heston, L. L., Litt, M., & Schellenberg, G. D. (1996). Gender difference in apolipoprotein E—associated risk for familial alzheimer disease: A possible clue to the higher incidence of alzheimer disease in women. *American Journal of Human Genetics*, *58*, 803–811.

Payne, A. H., & Hales, D. B. (2004). Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocrine Reviews*, *25*, 947–970.

Peedikayil-Kurien, S., Setty, H., & Oren-Suissa, M. (2022). Environmental experiences shape sexually dimorphic neuronal circuits and behaviour. *The FEBS Journal*. https://doi.org/10.1111/febs.16714

Penke, B., Paragi, G., Gera, J., Berkecz, R., Kovács, Z., Crul, T., & VÍgh, L. (2018). The role of lipids and membranes in the pathogenesis of Alzheimer's disease: A comprehensive view. *Current Alzheimer Research*, *15*, 1–22.

Perrin, R. J., Woods, W. S., Clayton, D. F., & George, J. M. (2000). Interaction of human α-synuclein and Parkinson's disease variants with phospholipids: Structural analysis using site-directed mutagenesis. *The Journal of Biological Chemistry*, *275*, 34393–34398.

Perrot-Sinal, T. S., Davis, A. M., & McCarthy, M. M. (2001). Developmental sex differences in glutamic acid decarboxylase (GAD65) and the housekeeping gene, GAPDH. *Brain Research*, *922*, 201–208.

Peters, S. A. E., Colantonio, L. D., Zhao, H., Bittner, V., Dai, Y., Farkouh, M. E., Monda, K. L., Safford, M. M., Muntner, P., & Woodward, M. (2018). Sex differences in high-intensity statin use following myocardial infarction in the United States. *Journal of the American College of Cardiology*, *71*, 1729–1737.

Phillips, G. R., Hancock, S. E., Jenner, A. M., McLean, C., Newell, K. A., & Mitchell, T. W. (2022). Phospholipid profiles are selectively altered in the putamen and White frontal cortex of Huntington's disease. *Nutrients*, *14*, 14.

Phoenix, C. H., Goy, R. W., Gerall, A. A., & Young, W. C. (1959). Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology*, *65*, 369–382. https://doi.org/10.1210/endo-65-3-369

Poeppl, T. B., Langguth, B., Rupprecht, R., Safron, A., Bzdok, D., Laird, A. R., & Eickhoff, S. B. (2016). The neural basis of sex differences in sexual behavior: A quantitative meta-analysis. *Frontiers in Neuroendocrinology*, *43*, 28–43.

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*, 1–21.

Pozzi, S., Benedusi, V., Maggi, A., & Vegeto, E. (2006). Estrogen action in neuroprotection and brain inflammation. *Annals of the New York Academy of Sciences*, *1089*, 302–323.

Prince, M., Ali, G. C., Guerchet, M., Prina, A. M., Albanese, E., & Wu, Y. T. (2016). Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimer's Research & Therapy*, *8*, 23.

Prinetti A., Chigorno V., Mauri L., Loberto N., Sonnino S. (2007) Modulation of cell functions by glycosphingolipid metabolic remodeling in the plasma membrane. *Journal of Neurochemistry.103* Suppl 1:113–125.

Proia, R. L., & Hla, T. (2015). Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy. *The Journal of Clinical Investigation*, *125*(4), 1379–1387. https://doi.org/10.1172/JCI76369

Prokopenko, D., Hecker, J., Kirchner, R., Chapman, B. A., Hoffman, O., Mullin, K., Hide, W., Bertram, L., Laird, N., DeMeo, D. L., Lange, C., & Tanzi, R. E. (2020). Identification of novel Alzheimer's disease loci using sex-specific family-based association analysis of whole-genome sequence data. *Scientific Reports*, *10*, 5029.

Ramanan, V. K., Castillo, A. M., Knopman, D. S., Graff-Radford, J., Lowe, V. J., Petersen, R. C., Jack, C. R., Mielke, M. M., & Vemuri, P. (2019). Association of apolipoprotein e ϵ4, educational level, and sex with tau deposition and tau-mediated metabolic dysfunction in older adults. *JAMA Netw Open*, *2*, e1913909.

Rappley, I., Myers, D. S., Milne, S. B., Ivanova, P. T., LaVoie, M. J., Brown, H. A., & Selkoe, D. J. (2009). Lipidomic profiling in mouse brain reveals differences between ages and genders, with smaller changes associated with α- Synuclein genotype. *Journal of Neurochemistry*, *111*, 15–25.

Rasia-Filho, A. A., Haas, D., de Oliveira, A. P., de Castilhos, J., Frey, R., Stein, D., Lazzari, V. M., Back, F., Pires, G. N., Pavesi, E., Winkelmann-Duarte, E. C., & Giovenardi, M. (2012). Morphological and functional features of the sex steroid-responsive posterodorsal medial amygdala of adult rats. *Mini Reviews in Medicinal Chemistry*, *12*, 12–1106.

Ratnakumar, A., Zimmerman, S. E., Jordan, B. A., & Mar, J. C. (2019). Estrogen activates Alzheimer's disease genes. *Alzheimer's & Dementia (New York, N. Y.)*, *5*, 906–917.

Rea, T. D., Breitner, J. C., Psaty, B. M., Fitzpatrick, A. L., Lopez, O. L., Newman, A. B., Hazzard, W. R., Zandi, P. P., Burke, G. L., Lyketsos, C. G., Bernick, C., & Kuller, L. H. (2005). Statin use and the risk of

incident dementia: The cardiovascular health study. *Archives of Neurology*, *62*, 1047.

Reekes, T. H., Higginson, C. I., Ledbetter, C. R., Sathivadivel, N., Zweig, R. M., & Disbrow, E. A. (2020). Sex specific cognitive differences in Parkinson disease. *NPJ Parkinson's Disease*, *6*, 7. https://doi.org/10.1038/s41531-020-0109-1

Rehbein, E., Hornung, J., Sundström, P. I., & Derntl, B. (2021). Shaping of the female human brain by sex hormones: A review. *Neuroendocrinology*, *111*, 183–206.

Riekkinen, P., Rinne, U. K., Pelliniemi, T. T., & Sonninen, V. (1975). Interaction between dopamine and phospholipids: Studies of the substantia Nigra in Parkinson disease patients. *Archives of Neurology*, *32*, 25.

Robak, L. A., Jansen, I. E., van Rooij, J., Uitterlinden, A. G., Kraaij, R., Jankovic, J., International Parkinson's Disease Genomics Consortium (IPDGC), Heutink, P., & Shulman, J. M. (2017). Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. *Brain*, *140*, 3191–3203.

Rockwood, K., & Darvesh, S. (2003). The risk of dementia in relation to statins and other lipid lowering agents. *Neurological Research*, *25*, 601–604.

Romeo, R. D., McCarthy, J. B., Wang, A., Milner, T. A., & McEwen, B. S. (2005). Sex differences in hippocampal estradiol-induced N-methyl-D-aspartic acid binding and ultrastructural localization of estrogen receptor-alpha. *Neuroendocrinology*, *81*, 81–399.

Roof, R. L., & Hall, E. D. (2000). Gender differences in acute CNS trauma and stroke: Neuroprotective effects of estrogen and progesterone. *Journal of Neurotrauma*, *17*, 367–388.

Rosenfeld, C. S. (2017). Brain sexual differentiation and requirement of SRY: Why or why not? *Frontiers in Neuroscience*, *11*, 632.

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and Biobehavioral Reviews*, *39*(100), 34–50.

Ruscica, M., Ferri, N., Santos, R. D., Sirtori, C. R., & Corsini, A. (2021). Lipid lowering drugs: Present status and future developments. *Current Atherosclerosis Reports*, *23*, 17.

Sá, S. I., Lukoyanova, E., & Madeira, M. D. (2009). Effects of estrogens and progesterone on the synaptic organization of the hypothalamic ventromedial nucleus. *Neuroscience*, *162*, 307–316.

Sá, S. I., & Madeira, M. D. (2005). Estrogen modulates the sexually dimorphic synaptic connectivity of the ventromedial nucleus. *The Journal of Comparative Neurology*, *484*, 68–79.

Sá, S. I., Teixeira, N., & Fonseca, B. M. (2018). Effects of tamoxifen on neuronal morphology, connectivity and biochemistry of hypothalamic ventromedial neurons: Impact on the modulators of sexual behavior. *Neurobiology of Disease*, *109*, 33–43.

Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., Kuder, J. F., Wang, H., Liu, T., Wasserman, S. M., Sever, P. S., & Pedersen, T. R. (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. *The New England Journal of Medicine*, *376*, 1713–1722.

Saldanha, C. J., Duncan, K. A., & Walters, B. J. (2009). Neuroprotective actions of brain aromatase. *Frontiers in Neuroendocrinology*, *30*(2), 106–118.

Samant, N. P., & Gupta, G. L. (2021). Novel therapeutic strategies for Alzheimer's disease targeting brain cholesterol homeostasis. *The European Journal of Neuroscience*, *53*, 673–686.

Sang, N., & Chen, C. (2006). Lipid signaling and synaptic plasticity. *The Neuroscientist*, *12*, 425–434.

Sarchielli, E., Comeglio, P., Filippi, S., Cellai, I., Guarnieri, G., Marzoppi, A., Cipriani, S., Vignozzi, L., Morelli, A., & Maggi, M. (2021). Neuroprotective effects of testosterone in the hypothalamus of an animal model of metabolic syndrome. *International Journal of Molecular Sciences*, *22*(4), 1589. https://doi.org/10.3390/ijms22041589

Sastry, P. S. (1985). Lipids of nervous tissue: Composition and metabolism. *Progress in Lipid Research*, *24*(2), 69–176.

Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. *Lancet (London, England)*, *397*(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

Schultz, B. G., Patten, D. K., & Berlau, D. J. (2018). The role of statins in both cognitive impairment and protection against dementia: A tale of two mechanisms. *Translational Neurodegeneration*, *27*(7), 5. https://doi.org/10.1186/s40035-018-0110-3

Segarra, A. C., & McEwen, B. S. (1991). Estrogen increases spine density in ventromedial hypothalamic neurons of peripubertal rats. *Neuroendocrinology*, *54*, 365–372.

Segatto, M., Giovanni, A., Di, M. M., & Pallottini, V. (2013). Analysis of the protein network of cholesterol homeostasis in different brain regions: An age and sex dependent perspective. *Journal of Cellular Physiology*, *228*, 1561–1567.

Setó-Salvia, N., Pagonabarraga, J., Houlden, H., Pascual-Sedano, B., Dols-Icardo, O., Tucci, A., Paisán-Ruiz, C., Campolongo, A., Antón-Aguirre, S., Martín, I., Muñoz, L., Bufill, E., Vilageliu, L., Grinberg, D., Cozar, M., Blesa, R., Lleó, A., Hardy, J., Kulisevsky, J., & Clarimón, J. (2012). Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. *Movement Disorders*, *27*, 393–399.

Seyfried, T. N., Choi, H., Chevalier, A., Hogan, D., Akgoc, Z., & Schneider, J. S. (2018). Sex-related abnormalities in substantia Nigra lipids in Parkinson's disease. *ASN Neuro*, *10*, 10.

Shepardson, N. E., Shankar, G. M., & Selkoe, D. J. (2011). Cholesterol level and statin use in Alzheimer disease: I. review of epidemiological and preclinical studies. *Archives of Neurology*, *68*(10), 1239–1244.

Sherwin, B. B. (2012). Estrogen and cognitive functioning in women: Lessons we have learned. *Behavioral Neuroscience*, *126*, 123–127.

Shibata, N., Kato, Y., Inose, Y., Hiroi, A., Yamamoto, T., Morikawa, S., Sawada, M., & Kobayashi, M. (2011). 4-hydroxy-2-nonenal upregulates and phosphorylates cytosolic phospholipase A2 in cultured Ra2 microglial cells via MAPK pathways. *Neuropathology*, *31*, 122–128.

Simons, M., Keller, P., Dichgans, J., & Schulz, J. B. (2001). Cholesterol and Alzheimer's disease: Is there a link? *Neurology*, *57*, 1089–1093.

Simón-Sánchez, J., Schulte, C., Bras, J. M., Sharma, M., Gibbs, J. R., Berg, D., Paisan-Ruiz, C., Lichtner, P., Scholz, S. W., Hernandez, D. G., Krüger, R., Federoff, M., Klein, C., Goate, A., Perlmutter, J., Bonin, M., Nalls, M. A., Illig, T., Gieger, C., … Gasser, T. (2009). Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nature Genetics*, *41*, 1308–1312.

Sipione, S., Monyror, J., Galleguillos, D., Steinberg, N., & Kadam, V. (2020). Gangliosides in the brain: Physiology, Pathophysiology and Therapeutic Applications. *Frontiers in Neuroscience*, *14*, 572965.

Skowronska-Krawczyk, D., & Budin, I. (2020). Aging membranes: Unexplored functions for lipids in the lifespan of the central nervous system. *Experimental Gerontology*, *131*, 110817.

Slotnick, S. D. (2021). Sex differences in the brain. *Cognitive Neuroscience*, *12*, 103–105.

Sobočanec, S., Balog, T., Kušć, B., Šverko, V., Šarić, A., & Marotti, T. (2008). Differential response to lipid peroxidation in male and female mice with age: Correlation of antioxidant enzymes matters. *Biogerontology*, *9*, 335–343.

Sobočanec, S., Balog, T., Šverko, V., & Marotti, T. (2003). Sex-dependent antioxidant enzyme activities and lipid peroxidation in ageing mouse brain. *Free Radical Research*, *37*, 743–748.

Sohrabji, F. (2015). Estrogen-IGF-1 interactions in neuroprotection: Ischemic stroke as a case study. *Frontiers in Neuroendocrinology*, *36*, 1–14.

Song, L., Mao, J., Wang, Q., Chen, A., Sun, R., Li, X., Luo, J., Zhao, P., Shi, Y., Su, Y., Liu, K., Yuan, F., Wang, S., Li, Y., Zhang, H., Yu, D., & Shi, H. (2022). Long-lasting and sex-dependent effects of Postweaning

swimming exercise on social dominance in adult mice. *Neuroscience*, *498*, 224–234.

Sonnino, S., Aureli, M., Grassi, S., Mauri, L., Prioni, S., & Prinetti, A. (2014). Lipid rafts in neurodegeneration and neuroprotection. *Molecular Neurobiology*, *50*, 130–148.

Sonnino, S., & Prinetti, A. (2012). Membrane domains and the lipid raft concept. *Current Medicinal Chemistry*, *20*, 4–21.

Sottero, B., Rossin, D., Poli, G., & Biasi, F. (2018). Lipid oxidation products in the pathogenesis of inflammation-related gut diseases. *Current Medicinal Chemistry*, *25*(11), 1311–1326. https://doi.org/10.2174/0929867324666170619104105

Spence, R. D., & Voskuhl, R. R. (2012). Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. *Frontiers in Neuroendocrinology*, *33*(1), 105–115.

Spiteller, G. (2002). Are changes of the cell membrane structure causally involved in the aging process? *Annals of the New York Academy of Sciences*, *959*, 30–44.

Spring, S., Lerch, J. P., & Henkelman, R. M. (2007). Sexual dimorphism revealed in the structure of the mouse brain using three-dimensional magnetic resonance imaging. *NeuroImage*, *35*, 35–1433.

Starčević, K., Filipović, N., Šperanda, M., Đidara, M., & Mašek, T. (2017). The influence of sex and gonadectomy on hepatic and brain fatty acid composition, lipogenesis and β-oxidation. *Journal of Animal Physiology and Animal Nutrition*, *101*, 649–657.

Steinberg, S., Stefansson, H., Jonsson, T., Johannsdottir, H., Ingason, A., Helgason, H., Sulem, P., et al. (2015). Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nature Genetics*, *47*, 445–447.

Stern, Y., Tang, M. X., Albert, M. S., Brandt, J., Jacobs, D. M., Bell, K., Marder, K., Sano, M., Devanand, D., Albert, S. M., Bylsma, F., & Tsai, W. Y. (1997). Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA*, *277*, 806–812.

Svennerholm, L., Boström, K., Fredman, P., Månsson, J. E., Rosengren, B., & Rynmark, B. M. (1989). Human brain gangliosides: Developmental changes from early fetal stage to advanced age. *Biochimica et Biophysica Acta*, *1005*, 109–117.

Svennerholm, L., Boström, K., Helander, C. G., & Jungbjer, B. (1991). Membrane lipids in the aging human brain. *Journal of Neurochemistry*, *56*, 2051–2059.

Svennerholm, L., Boström, K., Jungbjer, B., & Olsson, L. (1994). Membrane lipids of adult human brain: Lipid composition of frontal and temporal lobe in subjects of age 20–100 years. *Journal of Neurochemistry*, *63*, 1802–1811.

Swaab, D. F., Chung, W. C., Kruijver, F. P., Hofman, M. A., & Hestiantoro, A. (2003). Sex differences in the hypothalamus in the different stages of human life. *Neurobiology of Aging*, *24*(Suppl 1), S1–S19. https://doi.org/10.1016/s0197-4580(03)00059-9

Tabatadze, N., Huang, G., May, R. M., Jain, A., & Woolley, C. S. (2015). Sex differences in molecular signaling at inhibitory synapses in the hippocampus. *The Journal of Neuroscience*, *35*, 11252–11265.

Tadiri, C. P., Raparelli, V., Abrahamowicz, M., Kautzy-Willer, A., Kublickiene, K., Herrero, M. T., Norris, C. M., & Pilote, L. (2021). Methods for prospectively incorporating gender into health sciences research. *Journal of Clinical Epidemiology*, *129*, 191–197.

Tassoni, D., Kaur, G., Weisinger, R. S., & Sinclair, A. J. (2008). The role of eicosanoids in the brain. *Asia Pacific Journal of Clinical Nutrition*, *17*(Suppl 1), 220–228.

Teissier, T., Boulanger, E., & Deramecourt, V. (2020). Normal ageing of the brain: Histological and biological aspects. *Revue Neurologique (Paris)*, *176*, 649–660.

Thanky, N. R., Son, J. H., & Herbison, A. E. (2002). Sex differences in the regulation of tyrosine hydroxylase gene transcription by estrogen in the locus coeruleus of TH9-LacZ transgenic mice. *Brain Research. Molecular Brain Research*, *104*, 220–226.

Tipton, P. W., Bülbül, N. G., Crook, J. E., Quicksall, Z., Ross, O. A., Uitti, R. J., Wszolek, Z. K., & Ertekin-Taner, N. (2021). Effects of sex and APOE on Parkinson's disease-related cognitive decline. *Neurologia i Neurochirurgia Polska*, *55*, 559–566.

Trova, S., Bovetti, S., Bonzano, S., De Marchis, S., & Peretto, P. (2021). Sex steroids and the shaping of the peripubertal brain: The sexual-dimorphic set-up of adult neurogenesis. *International Journal of Molecular Sciences*, *22*(15), 7984. https://doi.org/10.3390/ijms22157984

Jessica Tulloch, Lesley Leong, Zachary Thomson, Sunny Chen, Eun-Gyung Lee, C. Keene D., Steven P. Millard, Chang-En Yu (2018) Glia-specific APOE epigenetic changes in the Alzheimer's disease brain. *Brain Research 1698*:179–186.

Tu-Sekine, B., Goldschmidt, H., & Raben, D. M. (2015). Diacylglycerol, phosphatidic acid, and their metabolic enzymes in synaptic vesicle recycling. *Advances in Biological Regulation*, *57*, 147–152. https://doi.org/10.1016/j.jbior.2014.09.010

Udagawa, J., & Hino, K. (2022). Plasmalogen in the brain: Effects on cognitive functions and behaviors attributable to its properties. *Brain Research Bulletin*, *188*, 197–202.

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. *International Journal of Geriatric Psychiatry*, *16*, 16–815.

Ugalde, C. L., Lawson, V. A., Finkelstein, D. I., & Hill, A. F. (2019). The role of lipids in -synuclein misfolding and neurotoxicity. *The Journal of Biological Chemistry*, *294*(23), 9016–9028.

Uhl, M., Schmeisser, M. J., & Schumann, S. (2022). The sexual dimorphic synapse: From spine density to molecular composition. *Frontiers in Molecular Neuroscience*, *15*, 818390.

Vallés, A. S., & Barrantes, F. J. (2022). The synaptic lipidome in health and disease. Biochimica et biophysica acta. *Biomembranes*, *1864*(11), 184033. https://doi.org/10.1016/j.bbamem.2022.184033

VanRyzin, J. W., Marquardt, A. E., Pickett, L. A., & McCarthy, M. M. (2020). Microglia and sexual differentiation of the developing brain: A focus on extrinsic factors. *Glia*, *68*, 1100–1113.

Venkateshappa, C., Harish, G., Mahadevan, A., Srinivas Bharath, M. M., & Shankar, S. K. (2012). Elevated oxidative stress and decreased antioxidant function in the human hippocampus and frontal cortex with increasing age: Implications for neurodegeneration in Alzheimer's disease. *Neurochemical Research*, *37*, 1601–1614.

Villa, A., Vegeto, E., Poletti, A., & Maggi, A. (2016). Estrogens, neuroinflammation, and neurodegeneration. *Endocrine Reviews*, *37*(4), 372–402.

Virmani, A., Pinto, L., Binienda, Z., & Ali, S. (2013). Food, nutrigenomics, and neurodegeneration—Neuroprotection by what you eat! *Molecular Neurobiology*, *48*, 353–362.

Vozella, V., Basit, A., Misto, A., & Piomelli, D. (2017). Age-dependent changes in nervonic acid-containing sphingolipids in mouse hippocampus. *Biochimica et Biophysica Acta. Molecular and Cell Biology of Lipids*, *1862*, 1502–1511.

Wallen, K. (2005). Hormonal influences on sexually differentiated behavior in nonhuman primates. *Frontiers in Neuroendocrinology*, *26*, 7–26.

Wallen, K. (2009). The organizational hypothesis: Reflections on the 50th anniversary of the publication of Phoenix, Goy, Gerall, and Young (1959). *Hormones and Behavior*, *55*(5), 561–565.

Wang, Y., Liu, L., Xiong, J., Zhang, X., Chen, Z., Yu, L., Chen, C., Huang, J., Zhang, Z., Mohmed, A. A., Lin, Z., Xiong, N., & Wang, T. (2012). Glucocerebrosidase L444P mutation confers genetic risk for Parkinson's disease in Central China. *Behavioral and Brain Functions*, *8*, 57.

Watzka, M., Bidlingmaier, F., Schramm, J., Klingmüller, D., & Stoffel-Wagner, B. (1999). Sex- and age-specific differences in human brain CYP11A1 mRNA expression. *Journal of Neuroendocrinology*, *11*, 901–905.

Wellman, C. L., Bollinger, J. L., & Moench, K. M. (2020). Effects of stress on the structure and function of the medial prefrontal cortex:

Insights from animal models. *International Review of Neurobiology*, *150*, 129–153. https://doi.org/10.1016/bs.irn.2019.11.007

Więckowska-Gacek, A., Mietelska-Porowska, A., Wydrych, M., & Wojda, U. (2021). Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. *Ageing Research Reviews*, *70*, 101397.

Wissman, A. M., May, R. M., & Woolley, C. S. (2012). Ultrastructural analysis of sex differences in nucleus accumbens synaptic connectivity. *Brain Structure & Function*, *217*, 181–190.

Witt, K. A., & Sandoval, K. E. (2014). Steroids and the blood-brain barrier: Therapeutic implications. *Advances in Pharmacology (San Diego, Calif.)*, *71*, 361–390. https://doi.org/10.1016/bs.apha.2014.06.018

Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. G., & Siegel, G. (2000). Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Archives of Neurology*, *57*, 1439–1443.

Wong, M. W., Braidy, N., Poljak, A., Pickford, R., Thambisetty, M., & Sachdev, P. S. (2017). Dysregulation of lipids in Alzheimer's disease and their role as potential biomarkers. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*, 810–827.

Wong, M. W. K., Braidy, N., Pickford, R., Vafaee, F., Crawford, J., Muenchhoff, J., Schofield, P., Attia, J., Brodaty, H., Sachdev, P., & Poljak, A. (2019). Plasma lipidome variation during the second half of the human life span is associated with age and sex but minimally with BMI. *PlosOne*, *14*, e0214141.

Woolley, C. S., Weiland, N. G., McEwen, B. S., & Schwartzkroin, P. A. (1997). Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: Correlation with dendritic spine density. *The Journal of Neuroscience*, *17*, 1848–1859.

Wooten, G. F., Currie, L. J., Bovbjerg, V. E., Lee, J. K., & Patrie, J. (2004). Are men at greater risk for Parkinson's disease than women? *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*, 637–639.

Wu, D. F., Lin, D., Lu, F., Liao, Q. C., Wu, Y. J., Wang, Z., Yu, K., Li, W. J., & Deng, J. L. (2020). Sex-specific influence of the SCARB1 Rs5888 SNP on the serum lipid response to atorvastatin in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Pharmacogenomics and Personalized Medicine*, *13*, 553–561. https://doi.org/10.2147/PGPM.S273346

Wu, G., Lu, Z.-H., Kulkarni, N., & Ledeen, R. W. (2012). Deficiency of ganglioside GM1 correlates with Parkinson's disease in mice and humans. *Journal of Neuroscience Research*, *90*, 1997–2008.

Xiao, S., Finkielstein, C. V., & Capelluto, D. G. (2013). The enigmatic role of sulfatides: new insights into cellular functions and mechanisms of protein recognition. *Advances in Experimental Medicine and Biology*, *991*, 27–40. https://doi.org/10.1007/978-94-007-6331-9_3

Xicoy, H., Wieringa, B., & Martens, G. J. M. (2019). The role of lipids in Parkinson's disease. *Cells*, *8*(1), 27. https://doi.org/10.3390/cells8010027

Xu, Q., Bernardo, A., Walker, D., Kanegawa, T., Mahley, R. W., & Huang, Y. (2006). Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. *The Journal of Neuroscience*, *26*, 4985–4994.

Xu, Y. H., Barnes, S., Sun, Y., & Grabowski, G. A. (2010). Multi-system disorders of glycosphingolipid and ganglioside metabolism. *Journal of Lipid Research*, *51*(7), 1643–1675. https://doi.org/10.1194/jlr.R003996

Yan, J., Sun, J., Huang, L., Fu, Q., & Du, G. (2014). Simvastatin prevents neuroinflammation by inhibiting N-methyl-D-aspartic acid receptor 1 in 6-hydroxydopamine-treated PC12 cells. *Journal of Neuroscience Research*, *92*, 634–640.

Yan, J., Xu, Y., Zhu, C., Zhang, L., Wu, A., Yang, Y., Xiong, Z., Deng, C., Huang, X. F., Yenari, M. A., Yang, Y. G., Ying, W., & Wang, Q. (2011). Simvastatin prevents dopaminergic neurodegeneration in experimental parkinsonian models: The association with anti-inflammatory responses. *PLoS One*, *6*, e20945.

Yin, F. (2022). Lipid metabolism and Alzheimer's disease: Clinical evidence, mechanistic link and therapeutic promise. *The FEBS Journal*, *290*, 1420–1453.

Yin, H., Xu, L., & Porter, N. A. (2011). Free radical lipid peroxidation: Mechanisms and analysis. *Chemical Reviews*, *111*(10), 5944–5972.

Zachry, J. E., Nolan, S. O., Brady, L. J., Kelly, S. J., Siciliano, C. A., & Calipari, E. S. (2021). Sex differences in dopamine release regulation in the striatum. *Neuropsychopharmacology*, *46*, 491–499.

Zampino, M., Polidori, M. C., Ferrucci, L., Neill, D. O., Pilotto, A., Gogol, M., & Rubenstein, L. (2022). Biomarkers of aging in real life: Three questions on aging and the comprehensive geriatric assessment. *GeroScience*, *44*, 2611–2622.

Zarrouk, A., Vejux, A., Mackrill, J., O'Callaghan, Y., Hammami, M., O'Brien, N., & Lizard, G. (2014). Involvement of oxysterols in age-related diseases and ageing processes. *Ageing Research Reviews*, *18*, 148–162.

Zhang, J., & Liu, Q. (2015). Cholesterol metabolism and homeostasis in the brain. *Protein and Cell*, *6*(4), 254–264. https://doi.org/10.1007/s13238-014-0131-3

Zhao, M., Woodward, M., Vaartjes, I., Millett, E. R. C., Klipstein-Grobusch, K., Hyun, K., Carcel, C., & Peters, S. A. E. (2020). Sex differences in cardiovascular medication prescription in primary care: A systematic review and meta-analysis. *American Heart Association*, *9*(11), e014742.

Zissimopoulos, J. M., Barthold, D., Brinton, R. D., & Joyce, G. (2017). Sex and race differences in the association between statin use and the incidence of Alzheimer disease. *JAMA Neurology*, *74*, 225–232.

Zucker, I., Prendergast, B. J., & Beery, A. K. (2021). Pervasive neglect of sex differences in biomedical research. *Cold Spring Harbor Perspectives in Biology*, *14*(4), a039156.

How to cite this article: Cuenca-Bermejo, L., Prinetti, A., Kublickiene, K., Raparelli, V., Kautzky-Willer, A., Norris, C. M., Pilote, L.; the GOING-FWD Consortium., & Herrero, M. T. (2023). Fundamental neurochemistry review: Old brain stories - Influence of age and sex on the neurodegeneration-associated lipid changes. *Journal of Neurochemistry*, *166*, 427–452. https://doi.org/10.1111/jnc.15834