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REVIEW

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

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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

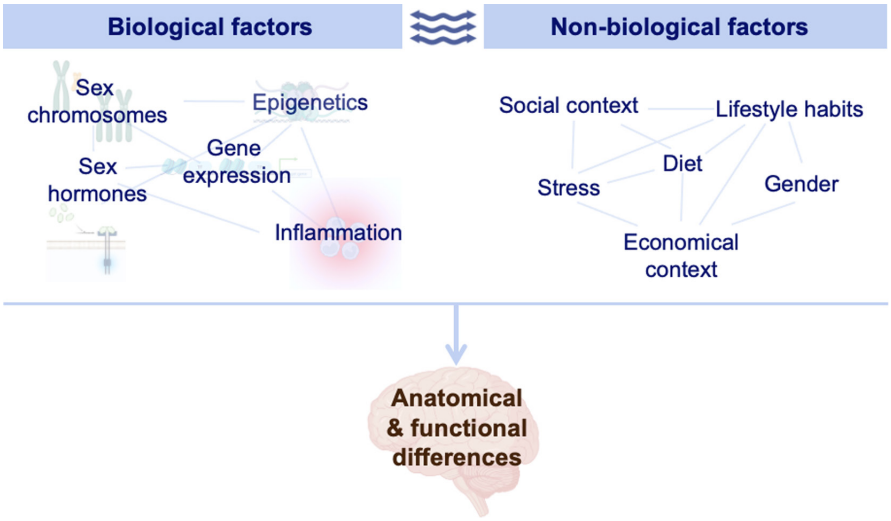


FIGURE 1 The interplay between biological and non-biological factors determines brain anatomy and circuits. Differences between males' and females' brains are stablished during the developmental period because of biological factors, including sex chromosomes and sex hormones. In the following periods 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

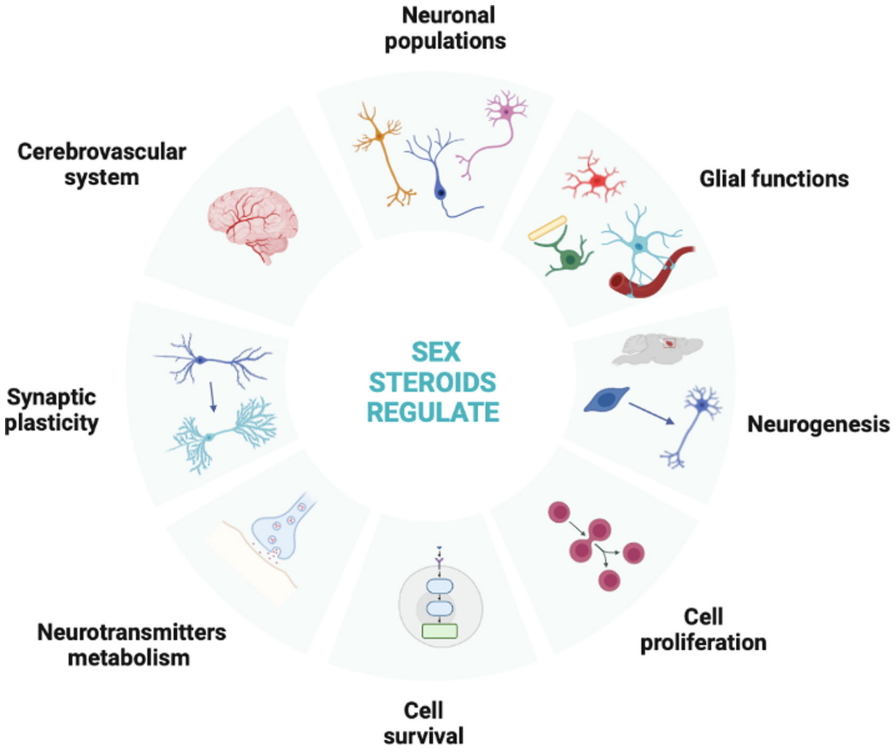


FIGURE 2 Sex steroids regulate a plethora of processes in the nervous system. Sex steroids have been shown to be involved in determining neuronal and glial populations and functions (Chesik & De Keyser, 2010; Gildawie et al., 2020; VanRyzin et al., 2020), synaptic plasticity (Leranth et al., 2004; Wissman 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.

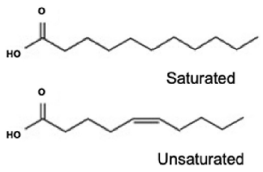
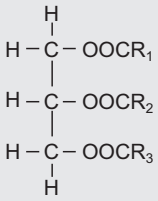
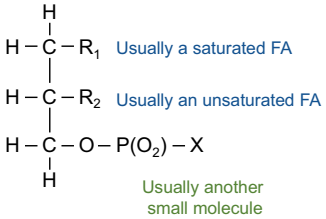
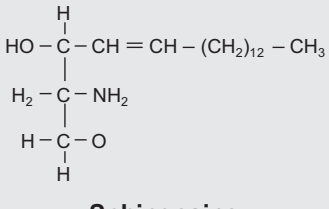
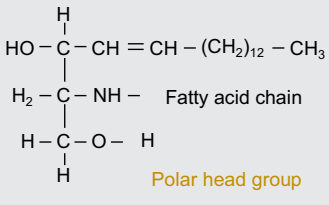
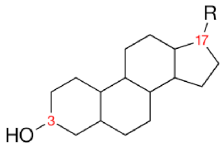
Lipid class	General structure	Examples	Function
FA	Carboxylic acids with hydrocarbonated chains (from 4 to 36 carbon atoms).  	Docosahexaenoic acid, linoleic acid, and arachidonic acid	Basic building blocks of more complex lipids, source of energy (via β-oxidation), membrane constituents, and regulation 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  	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**  **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.

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CONFLICT OF INTEREST STATEMENT

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

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No data are available.

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