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

KEYWORDS

Lipids; sex; aging; Alzheimer's disease; Parkinson's disease; statins.

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; PD, Parkinson's disease; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; PSEN, presenilin; PUFA, polyunsaturated fatty acid; SM, sphingomyelin.

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1. BACKGROUND

The continuous increment of the worldwide life expectancy has placed age as one of the main risk factors to develop several disorders that impacts our societies by means of diseases (Zampino *et a*l. 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 indicate that the disruption of lipid metabolism is a key contributor to different neurodegenerative processes, including dementia, AD and PD (Moll *et al*. 2020; Hallett *et al.* 2019; Moll *et al.* 2021; Grassi *et al.* 2020; Kao *et al.* 2020; McFarlane and Kędziora-Kornatowska 2019; Wong *et al.* 2017; Chiurchiù *et al.* 2022).

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; Zucker *et al.* 2021; Tadiri *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 the 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 about lipids and sex differences crosstalk. 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 disease, AD and PD. Finally, we analyzed the influence of sex in the lipid-reducing therapies with a focus on neurological events.

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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 o 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 (McCarthy 2020; Cerghet *et al*. 2006; Gegenhuber and Tollkuhn 2020; Gamache *et al.* 2020; Rosenfeld 2017; Hong and Reiss 2014).

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 stressed like nutrition and the existence of comorbidities (Mena and Bolte 2019; Mauvais-Jarvis *et al.* 2020). 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 in three 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 (Payne and Hales 2004; Barakat *et al.* 2016; Hanukoglu *et al.* 1977). Therefore, the brain can be affected by both, circulating sex hormones and the ones synthetized *in situ*.

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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 to 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 (Duka *et al.* 2000; Sherwin 2012; Derby *et al.* 2009; Ancelin *et al.* 2014; Pozzi *et al.* 2006). Several works have demonstrated as well an association between reduced testosterone levels and increased risk of AD (Gillett *et al.* 2003; Paoletti *et al.* 2004; Moffat *et al.* 2004); however, the decrease in androgens is less pronounced than the 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 and active role on it was already introduced in the late 1950's (Kolata 1979; Wallen 2009). Initial studies using guinea pigs demonstrated that the prenatal exposure to steroidal hormones at a specific time period during development was associated with sexual behavior (Phoenix *et al.* 1959). These findings were lately confirmed in other mammalian species, including rodents and nonhuman primates (Wallen 2005; Bakker 2022). Since then, differences between males and females in several brain structures have been demonstrated, such as the hypothalamus (Heck and 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 (McEwen *et al*. 2016; Bauer, 2023), the frontal cortex (Wellman *et al.* 2020; Ginder *et al.* 2022), the thalamus (Poeppl *et al.* 2016) and the cerebellum (Oguro *et al.* 1998; Gao *et al.* 2022). 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 (Kolata 1979; Gorski *et al.* 1978; Panzica and Melcangi 2016; Ruigrok *et al.* 2014; Gurvich *et al.* 2020; Coyoy *et al.* 2016).

Accumulating evidence indicate that sex steroids participate and set up sex differences in the brain developmental frame at different levels, including neuronal membrane organization (Baulieu and 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.

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Evidence supporting brain anatomical and structural changes across the hormonal fluctuation periods in humans have 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 (Perrot-Sinal *et al.* 2001; McCarthy *et al.* 2002). The dopaminergic and the noradrenergic systems are additional examples of sexually dimorphic pathways (Thanky *et al.* 2002; Kritzer and Creutz 2008; Zachry *et al.* 2021). The expression of tyrosine hydroxylase in the neurons of the Substantia Nigra, the ventral tegmental area and the locus coeruleus is sex-dependent (Ma *et al.* 2007; Brown *et al.* 2015a; Thanky *et al.* 2002; Luque *et al.* 1992). Another sexually dimorphic system is the one of 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 (2020).

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 and Galea 2008), number and density of dendrites (Segarra and McEwen 1991; Mathias *et al.* 2010), patterns and density of fibers (Madeira and Paula-Barbosa 1993) and neurogenesis (Blankers and Galea 2021; Duarte-Guterman *et al.* 2015), among others. In addition, accumulating evidence indicate that the hippocampus is a key player in the sex steroids synthesis (Hojo *et al.* 2009; Brandt *et al.* 2020; de Gall *et al.* 2021).

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 detail see (Hansberg-Pastor *et al*. 2015; Panzica and Melcangi 2016; Chowen *et al.* 2000; Kight *et al.* 2020; Uhl *et al.* 2022; DeCasien *et al.* 2022).

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3. BRAIN LIPIDS

The brain is the most lipid-rich organ and lipids account for at least 50% of its dry weight (Sastry 1985; O'Brien and Sampson 1965; Kao *et al.* 2020). 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 and 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 phosphatitylcholine (PC) and sphingomyelin (SM) (Nelson and 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.* 2015a; 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 crosstalk is the fact that cholesterol acts as precursor of sex steroids. Thus, altered cholesterol metabolism can promote detrimental effects on sex steroids functions and, consequently, in 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 acids 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.

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Table 1. Lipids in the brain and their main functions. FA = fatty acids; GL = Glycerolipids; GPL = glycerophospholipids; SL = sphingolipids.

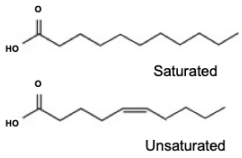
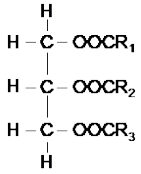
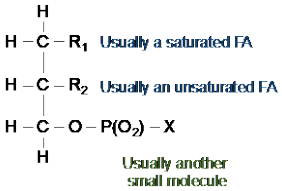
LIPID CLASS	GENERAL STRUCTURE	EXAMPLES	FUNCTION
FA	Carboxylic acids with hydrocarbonated chains (from 4 to 36 carbon atoms). 	Docosahexaenoic acid, linoleic acid and arachidonic acid	Basic building blocks of more complex lipids, source of energy (via β-oxidation), membrane constituents, regulation of cellular processes (e.g. gene expression) (Janssen and Kiliaan, 2014; Fritsche, 2015).
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 and 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, cardiolipin.	Basic components of cell membrane, regulation of cell processes (e.g. mitophagy), regulation of lipid metabolism (Kay and Grinstein, 2013; Antonny et al., 2015).
		Plasmalogens (pasmenyl ether-phospholipids).	Basic components of cell membrane, anti-apoptotic properties, regulation of inflammatory processes and key role in neurodegeneration (Udawa and Hino, 2022).

Table 1 continuation.

LIPID CLASS	GENERAL STRUCTURE	EXAMPLES	FUNCTION
SL	Sphingolipid building blocks	Sphingosine-1-phosphate	Regulation of cell signaling processes (e.g. cell survival) (Bartke and Hannun, 2009; Martin and Sospedra, 2014; Proia and Hla, 2015).
		Ceramide	Participates in lipid raft formation, regulation of the mitochondrial

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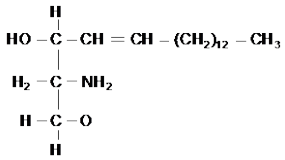
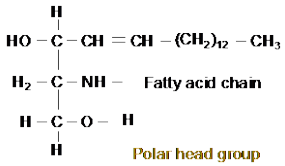
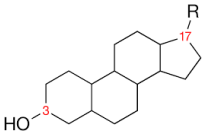
	 **Sphingosine**		respiratory chain and apoptosis (Xu et al., 2010; Mencarelli and Martinez-Martinez, 2013; Castro et al., 2014; Kogot-Levin and Saada, 2014).
		Sphingomyelin: phosphatidylcholine as polar head group	Major component of myelin (Xicoy et al., 2019)
	 **Ceramide**	Neutral glycosphingolipids (cerebrosides and globosides: one or more sugars as polar head group. E.g. glucosylceramide, galactosylceramide	Involved in intracellular transport and cell survival (Mesa-Herrera et al., 2019).
		Sulfated galactocerebrosides: esters of galactocerebrosides in which a sulfate group is placed at the C3. E.g. sulfatides	Participates in protein trafficking, immune reactions and neural plasticity (Xiao et al., 2013; Blomqvist et al., 2021).
		Gangliosides: polar head groups contain oligosaccharides and one or more terminal residues of N-acetylneuraminic acid (Neu5Ac). E.g. GM1, GM2, GD1a, GD1b.	Key role in lipid rafts formation, neurotransmission (Itokazu et al., 2018; Sipione et al., 2020).
Sterols	Steroid nucleus is the basic structure 	Cholesterol and cholesterol esters	Membrane properties (e.g. fluidity), hormones' precursos, lipid rafts formation, signaling processes. (Zhang and Liu, 2015; Kao et al., 2020).

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), compartmentalize and 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 and 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 (Sang and Chen 2006; Hillard 2018). Thus, it should not be

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surprising that dysregulation of lipid homeostasis has been related to the development of synaptopathies, loss of synaptic plasticity and neurological disorders (Vallés and Barrantes 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 (Woolley *et al.* 1997; Nilsen and Brinton 2002; Mukai *et al.* 2007; Kurz *et al.* 1986). In addition, a number of studies indicate that, in addition to regulatory effects, sex steroids are involved in sex differences in synapses (McEwen and 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 these areas that differed between males and females (Panzica and Melcangi 2016; Matsumoto and Arai 1983). Different authors have shown that estrogens mediate the synaptic plasticity in neurons in hypothalamic ventromedial nucleus (Sá *et al.* 2009; Sá *et al.* 2018; Lewis *et al.* 1995). In particular, the effect of estrogens in synaptic organization in this area was found sexually dimorphic the ventrolateral division of this nucleus: in rats, estrogens induced more dendritic synapses in females and more somatic synapses in males (Sá and Madeira 2005). In the same study, it was demonstrated that the number of dendritic synapsis changed in parallel with physiological variations in hormonal levels 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 and 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 and 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 (MacLusky *et al.* 2006; Leranth *et al.* 2004). However, the effect of estrogen was found just for females

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(Leranth *et al.* 2003; Lewis *et al.* 1995; MacLusky *et al*. 2006). Gall and collaborators (Gall *et al.* 2021) showed that synaptic plasticity need 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.* 2021). 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 that this is mediated via inositol triphosphate (IP3) generation and activation IP3 receptor activation (Huang and 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 and Simons 2010). This peculiar lipid composition configures intrinsic features that lead to the formation of small dynamic membrane domains known as lipid rafts. This micro- or nano-entities serve as platforms in which proteins can organize multiprotein complexes to favor their interactions at membrane level and promote signaling cascades (Sonnino and Prinetti 2012). In this sense, lipid rafts provide the adequate environment for sex hormones signaling via non-genomic pathways. Briefly, in the non-genomic mechanism, sex steroids bind to the cell membrane receptors, which localize in lipid rafts domains (Marin and Diaz 2018; Garza-Contreras *et al.* 2017). 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 and Diaz 2018; Spence and Voskuhl 2012; Sarchielli *et al.* 2021). 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

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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 (Moor *et al.* 2006; Calabrese *et al.* 2008; Venkateshappa *et al.* 2012). The imbalance in the redox status with aging towards 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 due to the presence of double bonds (Yin *et al.* 2011). LPO of PUFAs in cell membranes elevate 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 (Zarrouk *et al.* 2014; Sottero *et al.* 2017). 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 to 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 and 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 (Shibata *et al.* 2011; Di Domenico *et al.* 2017; De Virgilio *et al.* 2016). 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; Sobočanec *et al.* 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 and Hall 2000; Sobočanec *et al*. 2003).

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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 an 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 (Ooi *et al.* 2021; Skowronska-Krawczyk and Budin 2020; Naudí *et al.* 2015b; Svennerholm *et al.* 1989; Svennerholm *et al.* 1991; Svennerholm et al. 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).

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 (Starčević *et al.* 2017; Kitson *et al*. 2012). These diverse results might be due to 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; Więckowska-Gacek *et al.* 2021; Virmani *et al.* 2013). Importantly, different evidence point out that diet determines in a sex-specific manner the in brain PUFA content (Morselli *et al.* 2016; Morselli *et al.* 2014; Galli *et al.* 1970; Jacenik *et al.* 2021). 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; Tassoni *et al.* 2008; Kissoondoyal *et al.* 2021).

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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; Ostermann *et al.* 2017; Hennebelle *et al*. 2020). 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) which 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), 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 oxylipins levels in the brain (Gerges and 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.

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Table 2. Evidence for the effect of sex in lipid composition in physiological aging, AD and PD. 2D-TLC=Two-dimensional thin layer chromatography; HPTLC=2-D high-performance thin layer chromatography; GC=gas chromatography; GPL = glycerophospholipids; HPLC= High Performance Liquid Chromatography; HPLC-MS/MS= High Performance Liquid Chromatography tandem mass spectrometry; LC-MS/MS MS=mass spectrometry; SL=sphingolipids. AD=Alzheimer's disease; PD=Parkinson's disease; TLC=thin layer chromatography; TQ-MS=triple quadrupole mass spectrometer; UHPLC-MS/MS=Ultra-High Performance Liquid Chromatography tandem mass spectrometry.

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-6 J mice	MS	Chabrun et al., 2020
		C57Bl/6J mice	HPTLC, GC	Acaz-Fonseca et al., 2017
	SL	C57BL-6 J 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 disase	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

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 brain stem.

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On the other hand, a role for estradiol was suggested in the activity of phospholipids methyltransferase (assessed by the incorporation of 3H-methyl group incorporation 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 in humans and in experimental models, have evidenced sex-associated differences in the brain white matter content and structure, as well as in oligodendrocytes (Kaczkurkin *et al.* 2019; Ingalhalikar *et al.* 2014; Spring *et al.* 2007; Goldstein *et al.* 2001). Another line of evidence evaluating sphingolipidic 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 the 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 (Cerghet et al. 2006; Bayless and Daniel 2015; 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 a 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 to physiological aging, both in mice and in humans (Vozella *et al.* 2017; Couttas *et al.* 2018). 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

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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 with 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 brain. The trends of variations are very complex, and different for different brain areas, glycolipid species and age ranges (Ohsawa, 1989; Svennerholm, 1989; Svennerholm, 1991; Svennerholm, 1994; Barrier, 2007); 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 the adulthood (Palestini *et al.* 1997). Therefore, gangliosides changes along aging are sex-specific. A subsequent analysis showed that the gangliosides' specific differences when the two sexes were compared were due to changes in the ceramide moiety. Interestingly, they also discovered that gangliosides composition was different when the two hemispheres were compared just in females (Palestini *et al.* 1997).

4.4. Cholesterol and sterols metabolism

Several enzymes and proteins involvd 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 from estradiol circulating levels, whereas LDL glycosylation might be regulated by this hormone.

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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.* 2015a; 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 more pronounced in postmenopausal women (Díaz *et al.* 2018; Marin and Diaz 2018; Canerina-Amaro *et al.* 2017). 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 due to their modulatory role on lipid rafts in postmenopausal women (Marin and 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.* 2022). Its main histopathological features in the brain are the presence of extracellular Aβ plaques and intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau (Chen and 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 to genetic variants of three genes: the Aβ precursor protein (APP) and the presenilin

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genes 1 and 2 (PSEN1 and PSEN2) (Chen and Mobley 2019; Kloske and 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; Koran *et al.* 2017; Henderson and Buckwalter 1994). 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 to male sex (Davis *et al.* 2020; Claus *et al.* 1998; Ueki *et al.* 2001; Fernandez and Lapane 2002; Stern *et al.* 1997; Dubal 2020). 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) (Mielke *et al.* 2018; Ferretti *et al.* 2020; 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 peptides formation as well as in its toxicity (Kao *et al.* 2020). More specifically, altered lipid raft composition (e.g., high enrichment of GM1 ganglioside is 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 toxic soluble Aβ aggregates and of insoluble amyloid fibrils (Hartmann and Prinetti, 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 (Penke *et al.* 2018; Chew *et al.* 2020; Kao *et al.* 2020; Yin 2022). Here, we collect those studies that explore lipid-related changes in AD using a sex disaggregated approach.

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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; Hollingworth *et al.* 2011; Jones *et al.* 2011; Dong *et al.* 2017; El Gaamouch *et al.* 2016; 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 and 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 and Narayanaswami 2008; Xu *et al.* 2006; Kloske and Wilcock 2020). The APOE gene encodes for three protein isoforms: APOE2, APOE3 and APOE4. In particular, the aminoacids sequence of APOE4 provides conformational properties that are associated with reduced lipid transport in the CNS and lead to limited neuronal remodeling and repair (Nguyen *et al.* 2014; Li *et al.* 2002; Frieden *et al.* 2017; Chew *et al.* 2020).

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 3-fold increased risk (Chartier-hariln *et al.* 1994; Kloske and Wilcock 2020; de Rojas *et al.* 2021). Regarding sex differences, carrying the *APOE* ε4 allele (either heterozygous or homozygous) has a higher impact on the development and in the progression of the disease in the females compared to males, both in humans and in preclinical models (Payami *et al.* 1996; Bretsky *et al.* 1999; Buckley *et al.* 2019; Hohman *et al.* 2018; Ramanan *et al*. 2019; Altmann *et al.* 2014; Breitner *et al.* 1999; Mortensen and Høgh 2001; Martinsen *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 (Guo *et al.* 2017; Altmann *et al.* 2014). 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.

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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 (Chan *et al.* 2008; Fu *et al.* 2016; Apostolova *et al.* 2018).

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) (Kim *et al.* 2005; Fu *et al.* 2022). 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, in 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 the oestrous cycling (Logge *et al.* 2012). Evidence from human trials are aligned with these finding of experimental models. Some works have found that carrying the genetic variants of *ABCA7* related with AD development have a higher impact in women than in 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 estrogens levels and *ABCA7* gene variants showed a higher AD risk (Ratnakumar *et al.* 2019).

Altered lipid composition in AD brain from a sex perspective

Fatty acids

Little evidence exists on fatty acids 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 ω3 acids was 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.

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Sphingolipids

Studies using different experimental models demonstrated that the sphingolipid profile in the cortex showed a sex-specific pattern (den Hoedt *et al.* 2021; Barrier et al. 2010). 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 (Barrier *et al.* 2007; Kracun *et al.* 1992; Ariga 2017; Chan *et al.* 2012). 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.

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 rafts alterations contribute to progression of AD still needs to be clarified. Estrogen signaling occurs in lipid rafts and it is able to regulate lipid raft homeostasis (Marin *et al.* 2013; Canerina-Amaro *et al.* 2017; Maselli *et al.* 2015). Alterations at this level in women have been demonstrated during menopause and in AD, indicating that lipid rafts alterations in pathology are also influenced by sex (Marin and 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 (due to the death of dopaminergic neurons in the *Substantia Nigra pars compacta* (SNpc) and the loss of

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their terminals in the striatum) and ii) proteinaceous inclusions (enriched in misfolded α-synuclein) in neuronal cytoplasm, known as Lewy bodies (Cuenca *et al.* 2019; 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 (Kochmanski *et al.* 2022; Kalia and Lang 2015; 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 is 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 the sex (Haaxma *et al.* 2007; Gillies *et al*. 2014; Bakeberg *et al.* 2021). 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 to 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 (Ugalde *et al.* 2019; Perrin *et al.* 2000). Recently, several authors have recapitulated the changes in the composition and content of different lipids in PD patients (Ma *et al.* 2022; Xicoy *et al.* 2019; Galper *et al.* 2022). In this section we review the available evidence showing sex-related differences in the brain lipid changes in PD.

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 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)(Nalls *et al.* 2019; Galper *et al.* 2022).

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),

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ASAH (encoding for acid ceramidase), SREBF1 (encoding sterol regulatory element binding transcription factor 1) and DGKQ (encoding diacylglycerol kinase theta) (Galper *et al.* 2022; Gan-Or *et al.* 2013; Chang *et al.* 2017; de Carvalho Guimarães *et al.* 2012; Simón-Sánchez *et al.* 2009; Wang *et al.* 2012; Robak *et al.* 2017; Do *et al.* 2011). 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 of 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. Similarly 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 (Tipton *et al.* 2021; Kim *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.

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 (Xicoy *et al.* 2019; Galper *et al.* 2022). The number of studies incorporating the 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

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compared with their sex-matched controls. These results were in agreement to those previously described in studies where males and females were grouped (Wu *et al.* 2012; Hadaczek *et al.* 2015; Riekkinen *et al.* 1975). 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 include 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 to 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 (Kuang 2020; Samant and Gupta 2021; Kosowski *et al.* 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 (Wolozin *et al.* 2000; Rockwood and Darvesh 2003; Yan *et al.* 2014; Yan *et al.* 2011).

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For example, the use of statins was associated with improvement of cognitive decline (Schultz *et al.* 2018), the reduced risk of statin users to develop AD (Samant and 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, the inhibition of Aβ production (Simons *et al.* 2001; Dai *et al.* 2021). Conversely, others have not found significant contribution of statins in the neurodegenerative process (Rea *et al.* 2005) or have described harmful effects (Pasha *et al.* 2022; Dai *et al.* 2021; Jeong *et al.* 2021; Schultz *et al.* 2018). Altogether, these evidence point out that statins might have both positive and detrimental effects in 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.) (Shepardson *et al.* 2011; Ruscica *et al.* 2021; Karimi *et al.* 2023)

Similar to other scenarios, clinical trials to evaluate the safety and efficacy of lipid-lowering therapies have been predominantly performed in men (Khan *et al.* 2020; Faubion *et al.* 2019). Therefore, the current clinical guidelines barely consider the sex variable in the use of lipid-reducing agents as clinical interventions. Mercuro and collaborators collected the evidence regarding differences in the effect of lipid-lowering therapies in men and women (Mercuro *et al.* 2012). Here, we provide a list of trials that were released after their publication in which studies that have explored the pharmacological properties and the effect of lipid-lowering drugs applying the sex disaggregation (Table 3). Collectively, these evidence do not allow 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 statins therapy or have less likely to be prescribed with statins (Olmastroni *et al.* 2020; 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 due to 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 due to the fact that some comorbidities are more frequent in women than in men (e.g., hypothyroidism), which can be exacerbated by statins use (Brown *et al.* 2015b).

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Few studies have explored the sex differences in the neurological outcomes associated to lipid-lowering therapies. Indeed, we found just one trial matching these premise (Table 3)(Zissimopoulos *et al*. 2017). A recent preclinical study investigated the possible neuroprotective action of atorvastatin after the induction of cerebral microhaemorrhages (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 the 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, due to 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 to them. In this sense, the application of omics is of special relevant 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 to 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 in 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.*

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2022). In particular, we observed that research accounting for the gender effect is very limited and does not allow to reach consistent conclusions. At this point, it is worthy to mention that gender comprise 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 the real practical scenario. On the one hand, it will allow 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 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.

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Table 3. Studies evidencing sex-differences in the effects of lipid-lowering therapies. * studies in which neurological effects were explored

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 statins efficacy
Olmastroni *et al.* 2022	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.* 2020	Large-scale cohort using the UK Biobank and statistical modeling	*Participants:* 252 327 (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)

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Nanna *et al.* 2019	Statistical comparison of the PALM registry	*Participants*: 5 693 (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*: 27 564 (24.6% women) *Inclusion criteria*: participants 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 *	Examination of medical and pharmacy claims	*Participants:* 399 979 (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 6 large randomized clinical trials using patient-level data	*Participants*: 39 173 (23.4% women) *Inclusion criteria*: randomized clinical trials using data from patients following statins 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

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CONFLICT OF INTEREST

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

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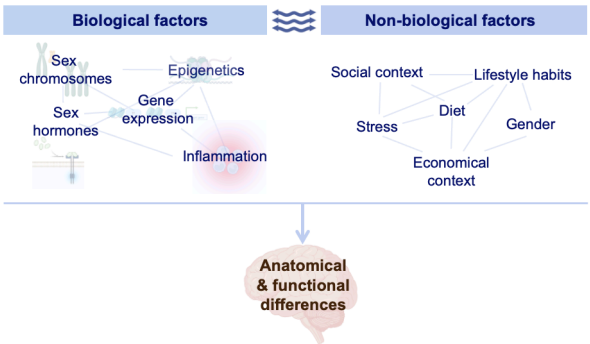

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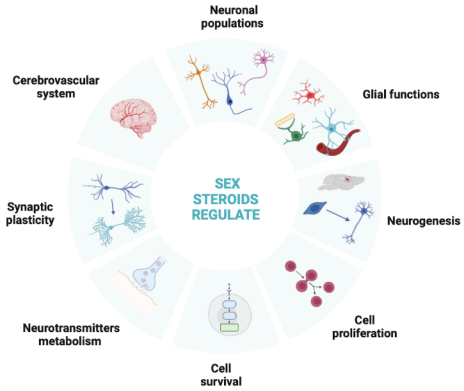

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