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# Lipid metabolism, remodeling and intercellular transfer in the CNS

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**Abstract**

Lipid metabolism encompasses the catabolism and anabolism of lipids, and is fundamental for the maintenance of cellular homeostasis, particularly within the lipid-rich central nervous system (CNS). Increasing evidence further underscores the importance of lipid remodeling and transfer within and between glial cells and neurons as key orchestrators of CNS lipid homeostasis. In this Review, we summarize and discuss the complex landscape of processes involved in lipid metabolism, remodeling and intercellular transfer in the CNS. Highlighted are key pathways, including those mediating lipid (and lipid droplet) biogenesis and breakdown, lipid oxidation and phospholipid metabolism, as well as cell–cell lipid transfer mediated via lipoproteins, extracellular vesicles and tunneling nanotubes. We further explore how the dysregulation of these pathways contributes to the onset and progression of neurodegenerative diseases, and examine the homeostatic and pathogenic impacts of environment, diet, and lifestyle on CNS lipid metabolism.

## [H1] Introduction

The mammalian CNS is highly enriched in lipids, which constitute at least 50% of its dry weight, surpassing the lipid content of the liver and heart, but remaining lower than that of adipose tissue[1,2]. Within the CNS, lipids such as cholesterol **[G]** and fatty acid (FA) **[G]** -containing lipid classes (such as phospholipids **[G]** and sphingolipids) have essential structural, functional, protective and metabolic roles that contribute to the maintenance of neuronal and glial cell physiology (**Supplementary Table 1**)(reviewed in REFs [1,3-6]). At the subcellular level, lipids are essential for maintaining cell membrane integrity and function, regulating signaling pathways, supporting organelle activity and organizing lipid rafts (dynamic lipid-rich microdomains in the plasma membrane that act as hubs for processes such as signal transduction and cell communication)[7-10]. At the cellular level, they play essential roles in energy storage and utilization and the stabilization of myelin sheaths, and facilitate processes such as oligodendrogenesis, neurogenesis and neuroprotection[1,11-14]. At the tissular level, lipids are vital for synaptogenesis, efficient neuronal communication and the preservation of the integrity of the blood-brain barrier (BBB)[5,15,16]. Finally, at the organ level, lipids are indispensable for brain development, cognitive function and processes involved in neuroinflammation and repair[17-20]. Not surprisingly, perturbations in lipid metabolism are increasingly recognized to disrupt cellular physiology and cause cytodegenerative effects in the CNS[1,21].

The CNS has evolved complex molecular pathways to maintain lipid homeostasis in glial and neuronal cells, or to restore it in response to pathological disruptions (reviewed in REFs [21,22]). In this context, the metabolism, remodeling (intracellular modification and redistribution) and intercellular transfer of lipids have emerged as important processes for ensuring the efficient utilization and turnover of lipids in the CNS. In this Review, we first explore key pathways involved in intracellular lipid metabolism and remodeling, including the biogenesis and breakdown of the most abundant lipids in the CNS (namely cholesterol, FAs and phospholipids) and lipid droplets **[G],** as well as the oxidation of lipids. We then discuss the intercellular transfer of lipids, mediated by lipoproteins **[G]** and

extracellular vesicles **[G]**. The impact of disease on these metabolic processes, as well as how disruptions in these processes contribute to the development and progression of neurodegenerative diseases, is also addressed. Finally, we examine how environment, diet, and lifestyle influence lipid metabolism, remodeling and transfer in the CNS and how these changes may affect CNS disease. We focus in particular on multiple sclerosis (MS), Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD) because of the strong experimental and genetic evidence linking disrupted lipid metabolism to the onset of these diseases and the similarities in their lipid-related pathophysiology.

## [H1] CNS lipid metabolism and remodeling

The CNS lipidome **[G]** is tightly regulated through coordinated bidirectional lipid fluxes between the periphery and the CNS, along with complex local metabolic and remodeling pathways. This section explores the metabolism and remodeling of cholesterol and FAs, which are essential components of the cellular membranes of neurons, glia and myelin. These lipids follow well-defined and key metabolic pathways within the CNS, making them fundamental to both CNS health and disease. We examine their synthesis, modification and degradation, as well the formation and breakdown of lipid droplets and the synthesis and remodeling of phospholipids. Disruptions in these processes are thought to contribute to the progression of CNS disorders.

### [H2] Cholesterol and fatty acid synthesis

The brain is the most cholesterol-rich organ in the body[23], and its cholesterol content is tightly regulated to safeguard normal brain function. Given that cholesterol is unable to freely traverse from the bloodstream into the CNS, the brain and spinal cord rely on de novo cholesterol synthesis in glial cells and, to a lesser extent, neurons (**Fig. 1**)[24]. The synthesis of cholesterol in the CNS is regulated by the sterol regulatory element-binding proteins (SREBP) and SREBP cleavage-activating protein (SCAP), which control the expression of genes involved in cholesterol production based on cellular

cholesterol levels (reviewed in REF [25]). In mammals, cholesterol biosynthesis mainly occurs between the perinatal period and adolescence, coinciding with the developmental ensheathment of axons by cholesterol-rich myelin[26]. Accordingly, deficits in cholesterol synthesis in mice result in a marked delay in myelination[12,27]. Once myelination is complete, cholesterol synthesis decreases and turnover slows[28,29], resulting in relatively stable brain cholesterol levels in adults[24]. Despite reduced turnover, cholesterol synthesis (primarily in astrocytes, which supply cholesterol to adjacent cells[30]) remains essential for CNS homeostasis in adults, with disruptions in this process linked to CNS complications. For example, reduced cholesterol synthesis is observed in postmortem brain tissue of HD patients[31]. Furthermore, in the aging human and mouse brain, a reduced cholesterol synthesis and progressively declining cholesterol content of myelin are associated with low-grade inflammation[30,32-35]. Finally, inhibition of cholesterol biosynthesis via statins has been shown to impair remyelination in adult mice following cuprizone-induced demyelination[36-38], andnegatively impact neuronal physiology in vitro by reducing their viability and promoting neurite loss[37,38]. However, other studies have reported neuroprotective and pro-regenerative effects of statins in humans and mice[39-42], and statins have been shown to reduce amyloidogenic processing of the amyloid precursor protein and formation of tau-containing neurofibrillary tangles in mouse models of AD[43-47]. The reasons for this discrepancy remain unclear but may include differences in model systems, statin concentrations, treatment windows and in the mechanisms of action of different statins[25,42,48].

Alongside cholesterol, and despite FAs being able to cross the BBB (**Box 1**), the CNS is capable of synthesizing saturated fatty acids (SFAs) **[G]** and monounsaturated fatty acids (MUFAs) **[G]** (**Fig. 1**), processes that (like cholesterol synthesis) are transcriptionally regulated by SREBP and SCAP (reviewed in REF [49]). The biosynthesis of SFAs and MUFAs occurs in the cytosol of both glial cells and neurons, with the SFA palmitate being a major intermediate product[49]. Successive elongation and desaturation steps, catalyzed by elongases (ELOVLs) and desaturases (Δ5, Δ6, and Δ9), can subsequently generate FAs with varying FA chain lengths and degrees of unsaturation (reviewed in REF [21]). ELOVLs add two-carbon units to the FA chain, while desaturases introduce double bonds at

specific positions within the carbon chain. While mammals cannot synthesize polyunsaturated fatty acids (PUFAs) **[G]** through de novo biogenesis, dietary PUFAs, such as linoleic acid and alpha-linolenic acid can be remodeled through elongation and desaturation. Supporting the importance of proper FA synthesis for CNS physiology, studies using genetic knockout models and pharmacological inhibitors have shown that CNS remyelination, adult neurogenesis, and developmental neuronal dendrite expansion are highly dependent on cell-autonomous FA synthesis by oligodendrocytes, neural stem cells (NSCs), and neurons, respectively[50-53]. On the other hand, studies have demonstrated that CNS demyelination increases the activity of ELOVL6 and the Δ9 FA desaturase stearoyl-CoA desaturase-1 (SCD1) in microglia and that this perturbs their pro-regenerative capacity and impairs remyelination[19,54]. Similarly, disease-associated elevations in SCD1 activity have been reported to impair regulatory T cell differentiation[19,55], suppress NSC proliferation[56], and promote the pathogenic processing of neuronal α-synuclein (α-syn; a protein closely linked to PD, where its abnormal aggregation drives neuronal dysfunction and cell death)[57]. These detrimental changes were found to enhance neuroinflammation and neurodegeneration in animal models of MS, AD, and PD[55-57]. Why SCD1 and ELOVL6 abundance is enhanced in these disorders is unclear but the increase may reflect compensation for the loss of long-chain MUFAs or altered lipid homeostasis due to disease-related metabolic changes (reviewed in REFs [21,58]). Overall, these studies underscore the important role of cholesterol and FA synthesis in maintaining and restoring CNS homeostasis, while demonstrating that disease-associated increases in FA elongation and desaturation are detrimental.

### [H2] Cholesterol and fatty acid oxidation

As compared to other tissues, the CNS is highly enriched in PUFAs (reviewed in REF [21]). This abundance can be explained by the essential role of PUFAs in supporting the structure and function of neuronal and glial cell membranes, and acting as precursors to signaling molecules such as endocannabinoids (reviewed in REF [59]). The function of PUFAs in the CNS is highly dependent on their oxidation, a form of lipid remodeling. This can occur non-enzymatically, when oxidants such as reactive oxygen species (ROS) interact with the carbon-carbon double bonds in PUFAs, a process

known as lipid peroxidation, or enzymatically, through the regulated conversion of PUFAs to their oxidized forms by enzymes such as lipoxygenases, cyclooxygenases or cytochrome P450 enzymes (reviewed in REF [21]) (**Fig. 1**). Enzymatic oxidation of PUFAs results in the formation of lipid mediators such as prostaglandins, eicosanoids and specialized pro-resolving mediators (SPMs) — so called bioactive lipids[60,61] — that play important roles in cell signaling events related to CNS disease progression and resolution. In this context, oxygenated ω6 and ω3 PUFAs, which differ in having have their first double bond at the sixth and third carbon atom from the methyl end, are generally regarded as harmful and benign, respectively[21,60,61]. However, exceptions to this simplified categorization exist; for instance, disease- or age-related reductions in lipoxin A4 — a bioactive lipid formed through the oxidation of the ω6 PUFA arachidonic acid (ARA) — exacerbate astrocyte, microglia, and monocyte activation, impair neuronal function and promote T-cell infiltration and encephalitogenicity within the CNS of mice and humans[62-64]. The interaction of oxidized PUFAs with specific receptors, along with factors such as their concentration, tissue and cellular context, and the disease state and stage during which they are generated, collectively determine their eventual impact in the CNS (reviewed in REFs [61,65]). In contrast to the controlled enzymatic oxidation of PUFAs, the uncontrolled peroxidation of membrane PUFAs in phospholipids driven by excessive ROS production in CNS disorders, leads to membrane dysfunction and iron-dependent necrotic cell death, a process known as ferroptosis (reviewed in REF [66]). Such oxidized phospholipids have been shown to be associated with neuroinflammation and to compromise the viability of neurons and oligodendrocytes in various CNS disorders[67,68].

Similar to PUFAs, cholesterol is highly susceptible to oxidative modification through both enzymatic and non-enzymatic pathways, leading to the formation of oxysterols that have pleiotropic functions (**Fig. 1**). Cytochrome P450 46A1 (CYP46A1)-mediated oxidation of cholesterol is a key homeostatic pathway in neurons, leading to the formation of 24(S)-hydroxycholesterol (24S-OHC), which readily diffuses across the BBB for disposal[24,69,70]. Since unmodified cholesterol cannot freely cross the BBB, this pathway is essential for cholesterol turnover in the CNS. Brain cholesterol can also be oxidized by

CYP27A1, expressed in neurons and glial cells, to form 27-OHC, which is also capable of crossing the BBB[71]. Alongside regulating cholesterol flux out of the brain, 24S-OHC and 27-OHC control the metabolism and intracellular transfer of other CNS lipids through the activation of astrocytic nuclear liver X receptors (LXRs)[71,72], as discussed in later sections. Even though these oxysterols are essential for CNS homeostasis, substantial evidence indicates that they can also promote disease progression in individuals with AD and AD models by enhancing neuroinflammation and increasing amyloid β (Aβ) and hyperphosphorylated tau levels[73-76]. They have also been shown to promote lysosomal membrane permeabilization-mediated pyroptosis and to negatively affect morphology and synaptic function in hippocampal neurons[77-79]. A recent study further revealed that 27-OHC promotes oligodendrocyte precursor cell (OPC) differentiation while simultaneously exhibiting toxicity towards immature oligodendrocytes, which was found to impair cognitive performance in mice[80]. The contrasting homeostatic and disease-promoting effects of these oxysterols are poorly understood, but it is hypothesized that disease-associated elevations contribute to the detrimental impact of oxysterols in CNS disorders. In addition to 24S-OHC and 27-OHC, various other oxysterols are present in the brain, arising from the auto-oxidation of cholesterol induced by compounds such as free radical species. This results in the formation of oxysterols such as 7α-OHC, 7β-OHC, 25-OHC, and 7-ketocholesterol (7-KC). Among these, 7-KC stands out as one of the most abundant, biologically active, and toxic oxysterols in the CNS (reviewed in REFs [81,82]).

In conclusion, the remodeling of FAs and cholesterol through oxidation generates oxygenated lipids, whose effects on CNS diseases are shaped by their abundance and by the mode of oxidation (enzymatic vs. non-enzymatic).

**[H2] Lipid droplet anabolism and catabolism**

In addition to their oxidation, FAs and cholesterol can be remodeled to produce a variety of other lipids with important cellular functions. These include neutral lipids, such as cholesteryl esters (CEs), diacylglycerols (DAGs) and triacylglycerols (TAGs), which can be contained within lipid droplets. Lipid

droplets are dynamic intracellular organelles composed of a hydrophobic core of neutral lipids, surrounded by a phospholipid monolayer. This monolayer is embedded with lipid droplet-associated proteins (LDAPs) that regulate lipid droplet function, of which perilipins (PLINs) represent the largest family[83]. Although the primary role of lipid droplets is the storage of energy (in the form of lipids), emerging research has revealed that lipid droplets play an essential role in intracellular signaling and metabolism by establishing functional contact sites with other organelles, such as mitochondria and the endoplasmic reticulum (ER), to facilitate metabolic crosstalk and regulation[84,85]. While the quantities of lipid droplets present in the healthy CNS are typically low, substantial accumulations resulting from an imbalance between lipid uptake, synthesis, and mobilization, are observed in the aging brain and in neurodegenerative disorders such as MS, AD, PD and HD, primarily in glial cells[86-88]. This dysregulation can arise from disease-associated changes in lipid droplet formation and breakdown[19,89,90].

Lipid droplet biogenesis begins at the ER, where neutral lipids are synthesized primarily through the actions of acyltransferases[91]. These enzymes catalyze the esterification of DAGs, which are derived from the breakdown of phospholipids or through de novo synthesis, and cholesterol with fatty acyl-CoA, forming TAGs and CEs, respectively. As these neutral lipids accumulate in the ER membrane, they promote localized lipid droplet formation, resulting in the budding and release of lipid droplets into the cytosol. Once in the cytoplasm, lipid droplets can expand by incorporating additional neutral lipids or by fusing with other lipid droplets. Aberrant lipid droplet formation in the CNS has been suggested to be linked to neurodegenerative disease, with the most compelling evidence for this in AD. Specifically, the apolipoprotein E4 (*APOE4*) allele, the strongest genetic risk factor for AD, promotes lipid droplet formation in both glial cells and neurons[92,93]. This increase in lipid droplet formation is thought to be driven, at least in part, by the upregulation of genes encoding proteins involved in lipid synthesis, such as acyl-CoA synthetase, which plays an essential role in the generation of fatty acyl-CoA[93].

During cell growth or in situations of energy deprivation, lipid droplets can be mobilized and broken down for energy production and the synthesis of membrane components and signaling molecules (reviewed in REF [94]). Breakdown of lipid droplets occurs through two main pathways: lipolysis and lipophagy (**Fig. 1**). Lipolysis involves the hydrolysis of TAGs into free FAs and glycerol by the consecutive actions of adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL). The importance of lipolysis for CNS function is demonstrated by recent findings that microglia in actively demyelinating lesions from people with MS show increased abundance of PLIN2, which inhibits lipolysis-mediated degradation of lipid droplets in these cells[95]. In preclinical models of MS, loss of PLIN2 reduced lipid droplet accumulation and induced a less-inflammatory microglia phenotype, thereby improving remyelination. These findings position PLIN2 as an LDAP that prevents lipid droplet degradation, similar to PLIN5, whose interaction with ATGL inhibits lipid droplet lipolysis[96]. The molecular drivers of the increased PLIN2 abundance in microglial lipid droplets during CNS demyelination remain unclear, but it is possible that CNS inflammation increases microglial PLIN2 expression[97]. This may be a protective response, because blocking ATGL-mediated breakdown of lipid droplets in microglia has recently been shown to alleviate neuroinflammatory and behavioural responses to lipopolysaccharide[98], suggesting that PLIN2-mediated inhibition of lipolysis during demyelination protects against excessive neuroinflammation. This feedback mechanism may be beneficial early after demyelination but could become detrimental during chronic demyelination, when abundant microglial lipid droplet formation is evident and associated with the induction of a harmful foamy microglia phenotype[19,54,89,99]. Neurons also express an additional specific lipid hydrolase, DDHD domain-containing 2 (DDHD2), which initiates lipolysis independently of ATGL and whose deficiency is linked to neuronal TAG deposition and hereditary spastic paraplegia[100]. However, the functional relevance of neuronal lipolysis remains unclear, as neurons typically do not form abundant lipid droplets[101].

In addition to lipolysis, lipid droplets can be degraded by a specific form of autophagy **[G]**, called lipophagy[102], a process that has gained substantial attention for its role in driving lipid metabolism in

the CNS (reviewed in REFs [103-105]). The autophagic degradation of lipid droplets involves their sequestration into autophagosomes, which subsequently fuse with lysosomes for degradation by lysosomal acid lipases (**Fig. 1**). Disruption of autophagy is an important pathological hallmark of various neurodegenerative conditions and aging, and increasing evidence suggests that impaired lipophagy may underlie abnormal lipid droplet accumulations in these conditions. For example, it was recently demonstrated that macrophages and microglia in active lesions of people with MS, which contain abundant remnants of intracellular myelin debris, exhibit signs of impaired lipophagy[106], leading to excessive lipid droplet accumulation and the adoption of a highly inflammatory, repair-inhibitory phagocyte phenotype. Inducing lipophagy with the autophagy activator trehalose reversed this harmful metabolic and inflammatory microglia phenotype, and promoted remyelination in preclinical models of MS. A direct link between impaired lipophagy and HD has also been reported: Huntingtin (HTT), the gene product responsible for HD (and which in its mutated form creates toxic aggregates that cause neuronal damage[107]) has been shown to function as a scaffold protein for the selective autophagy of lipid droplets[108]. By physically interacting with the autophagy cargo receptor p62 to facilitate its association with the autophagosome, HTT was found to be essential for at least three types of selective autophagy: lipophagy, mitophagy, and aggrephagy. Accordingly, loss of *Htt* in mice led to increased sensitivity to lipid challenges and a more pronounced accumulation of lipid droplets.

The fate of the lipids released by lipolysis and lipophagy is multifaceted. Once lipid droplet-associated neutral lipids are converted to free FAs, these can be degraded through mitochondrial β-oxidation **[G]** to meet cellular energy needs[102,109]. The acetyl-CoA that is produced from this β-oxidation could subsequently be utilized for de novo lipogenesis[110]. Alternatively, lipid droplet processing via lipophagy and lipolysis can facilitate the intercellular transfer of free cholesterol and FAs[111,112]. Notably, recent findings indicate that enhancing lipophagy promotes microglia lipid efflux within demyelinating brain lesions[106]. Catabolism of lipid droplets can also release or lead to the generation of signaling lipids. For example, unmodified free FAs may serve as endogenous ligands for

peroxisome proliferator-activated receptors (PPARs)[55,113], while oxidized PUFAs are potent signaling molecules[60,61]. Finally, lipid droplets can act as a readily available lipid reservoir, from which lipids can be released and used for membrane formation[114]. Collectively, these findings underscore the important roles of lipid droplet catabolism and anabolism in controlling lipid remodeling in the CNS. Tracer lipidomics **[G]** studies are, however, required to fully define the fate of the lipids released by lipolysis and lipophagy.

**[H2] Phospholipid synthesis and remodeling**

Phospholipids, including phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs), are key components of cellular membranes in the CNS, ensuring structural integrity, fluidity, and proper membrane functionality (reviewed in REF [115]). Their de novo synthesis occurs in all cell types via the Kennedy pathway, which converts choline and ethanolamine through successive enzymatic steps into PC and PE, respectively (**Fig. 1**)[116]. The final enzymatic step in this pathway involves the addition of a DAG, which can be synthesized de novo from glycerol-3-phosphate (G3P) or derived from the catabolism of existing phospholipids or TAGs stored in lipid droplets, among other sources (reviewed in REF [117]). The composition of the DAG molecule that is added, which is defined by the two FAs that are esterified to its glycerol backbone, directly influences the type of phospholipid that is synthesized, providing a form of lipid remodeling and diversifying the lipidome at the phospholipid level. Despite the abundance and tremendous compositional diversity of phospholipids in the CNS[6], direct evidence linking disturbances in the Kennedy pathway to glial cell and neuronal dysfunction in neurological disorders is currently lacking. Choline supplementation studies, however, suggest that limited availability of the substrates of the Kennedy pathway may be a key factor driving chronic neuroinflammation and failure of repair in preclinical MS models[118]. The quantity and composition of PCs and PEs are further known to impact glial cell and neuronal activity, plasticity, and survival[1,119-122], and alterations in the levels and composition of these phospholipids are associated with the pathology of most neurodegenerative disorders[1,68,123]. Notably, phospholipid synthesis also facilitates the formation of the autophagosomes that engulf organelles during autophagy[124]. Hence, in addition

to the active remodeling of the phospholipidome, the Kennedy pathway may indirectly affect lipid remodeling by influencing lipophagy.

The highly diverse and asymmetrical distribution of FA chains in phospholipids cannot be fully achieved by de novo synthesis via the Kennedy pathway. Instead, phospholipids in cellular membranes are postulated to be metabolically active and — in a process known as the Lands cycle — to continuously undergo deacylation and reacylation reactions. This results in the dynamic incorporation of PUFAs, particularly ARA and docosahexaenoic (DHA), into the phospholipids (reviewed in REF [125]). Mechanistically, the FA chains of de novo-synthesized phospholipids are hydrolyzed by divergent phospholipase A2 (PLA2) isoforms, generating lysophospholipids. These lysophospholipids are then reacylated by lysophospholipid acyltransferases (LPLATs), resulting in the incorporation of a new FA and the formation of a new phospholipid (**Fig. 1**). Reflecting its high activity level in the brain[126-128], alterations in the Lands cycle have increasingly been linked to disruptions in CNS homeostasis. For example, elevated PLA2 activity is associated with neuroinflammation, neurodegeneration, and cognitive deficits in mouse models of AD, PD, and MS, and in people with MS[129-135]. Interestingly, Aβ has been shown to enhance PLA2 levels, which may, at least in part, contribute to Aβ toxicity[133,134]. Conversely, loss of the *PLA2G6* isoform shortens lifespan, impairs synaptic transmission, promotes α-syn aggregation, and induces neurodegeneration in cell culture and animal models of PD[136,137], potentially by causing ER stress[138], while, *PLA2G6* mutations are associated with infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), and familial type 14 PD (PARK14)[139,140]. The dual harmful and benign roles of PLA2 isoforms remain poorly understood, but could reflect disease stage-dependent changes in PLA2 isoform abundance and isoform substrate specificity[141,142]. In contrast to PLA2 isoforms, research on LPLATs in CNS disease is sparse. *LPCAT1* is elevated in postmortem brain tissue from people with PD, and its suppression reduces α-syn accumulation and toxicity in a human PD cell culture model[143]. Furthermore, overexpression of LPEAT2, which uses DHA as a substrate, induces necrotic cell death in neuronal cells in vitro[144]. Collectively, ample evidence suggests that the Lands cycle is dysregulated

in various CNS disorders, though the mechanisms and implications of this remain unclear. Future studies should explore whether altered Lands cycle activity arises from disease-related changes in the compositional requirements of membrane phospholipids, serves to detoxify peroxidated membrane phospholipids, or reflects a need to generate lipid signaling metabolites. Notably, while outside the scope of this review, lipid remodeling similar to that seen in phospholipids is involved in the metabolism of many other lipid classes, underscoring the complexity and importance of these processes in maintaining cellular function in the CNS[145].

## [H1] Intercellular lipid transfer in the CNS

The ability of astrocytes and microglia to supply neurons and oligodendrocytes with lipids has been appreciated for many years[146-148]. However, emerging evidence has indicated that this intercellular lipid shuttling is not unidirectional, with neurons also being able to transfer lipids to astrocytes[101]. The most well-known process driving intercellular lipid transfer in the CNS is lipoprotein-mediated lipid flux, in which astrocytes and microglia synthesize and secrete lipoprotein particles that are composed of cholesterol and a neutral lipid core, and are surrounded by a phospholipid monolayer and apolipoproteins, primarily APOE (reviewed in REF [149]). Neurons and oligodendrocytes take up these particles and utilize the lipids for dendrite and axonal growth, synapse formation and communication, and myelin membrane maintenance and formation[146-148,150]. While they can also use these lipids as an energy source, this is likely to be limited due to their relatively low capacity for β-oxidation as compared to glia[151]. The essential role of lipoprotein-mediated lipid flux for CNS function is made particularly evident by studies of AD, where genetic variants of *APOE* and triggering receptor expressed on myeloid cells 2 (*TREM2*), encoding a receptor involved in the uptake of lipidated APOE, disrupt CNS lipid metabolism and drive disease progression (**Box 2**). Alongside lipoproteins, emerging evidence suggests that other mechanisms also control intercellular lipid fluxes in the CNS, including extracellular vesicles (EVs). In this section, we will discuss the key role of these intercellular lipid transfer mechanisms in maintaining CNS homeostasis and how perturbations in their activity can drive CNS pathologies.

**[H2] Lipid transfer between glia and neurons**

Glia-to-neuron lipid transfer plays an essential role in ensuring proper neuronal function, with the release of lipidated APOE by glial cells, followed by its uptake by neurons, being well-documented (reviewed in REFs [152,153]). Consistent with this, astrocyte-specific deficiency of *Scap*, a key regulator of de novo lipid biosynthesis (**Fig. 2**), impairs presynaptic terminal development, reduces neurite outgrowth, and leads to behavioral and motor defects in mice in vivo[154,155]. Similarly, astrocytes in a mouse model of HD exhibit impaired cholesterol biosynthesis and secrete reduced levels of APOE-bound cholesterol, which hinders neurite outgrowth and synaptic activity[156]. Enhancing astrocytic lipid biosynthesis and efflux was found to reverse these neuronal dysfunctions[156].

Studies also indicate that neuron-to-glia lipid transfer is a continuous and essential process in the CNS. The transfer of neuron-derived 24S-OHC to astrocytes activates APOE-mediated cholesterol efflux in these cells through an LXR-regulated pathway[72]. This 24S-OHC flux is likely to serve as a mechanism for neurons to communicate their cholesterol requirements to astrocytes, as astrocytic APOE-associated cholesterol is a major source of cholesterol for neurons. More recent studies indicate that neurons also transfer FAs to astrocytes[90,157], which is important because neurons typically lack the machinery to form lipid droplets (and thus to store FAs)[101]. Genetic and pharmacological studies have shown that, under homeostatic conditions, astrocytes take up blood glucose, convert it to lactate and transfer it to neurons via the monocarboxylate transporter[157]. Neurons metabolize the lactate to produce acetyl-CoA, a key substrate for energy production and de novo FA synthesis. The neurons maintain a stable and healthy FA lipidome by exporting excess FAs to astrocytes, which oxidize these lipids for energy[157]. It has been shown that elevated ROS levels promote the use of glial lactate to fuel neuronal lipogenesis, resulting in the formation of peroxidated FAs that are exported to, stored in, and catabolized by astrocytes[157]. While transient increases in ROS and peroxidated lipids can be buffered by astrocytes, the authors hypothesized that chronic and excessive ROS release, such as that seen in some CNS disorders, could overwhelm this

system, leading to astrocyte dysfunction and neurodegeneration. They further showed that neuron–glia lipid transfer and astrocytic lipid droplet formation depend on APOE. Notably, APOE4 was less efficient in facilitating neuron–glial lipid transfer and impaired the formation of lipid droplets in glial cells as compared to other APOE isoforms. This provides a molecular rationale for the increased neuronal lipid peroxidation observed in individuals with AD that carry *APOE4* alleles[157]. Supporting this notion, another study demonstrated that APOE4 hinders neuronal FA sequestration in lipid droplets, impairs the flux of lipid droplet-associated FAs from neurons to astrocytes, and reduces FA oxidation in astrocytes[158].

A recent study showed that lipid fluxes between neurons and astrocytes are also essential for protection against the adverse effects of neuronal hyperactivity[159], a hallmark of neurological disorders such as AD[160]. Hyperactive neurons, displaying increased lipid peroxidation[161,162], were found to avoid lipid toxicity by transferring toxic lipid intermediates to astrocytes (**Fig. 2**)[159]. Specifically, the hyperactive neurons released toxic lipids, including peroxidated FAs, encapsulated within APOE lipoproteins, which adjacent astrocytes endocytosed and incorporated into lipid droplets. The transferred FAs were used as metabolic intermediates for increased mitochondrial β-oxidation and detoxification in astrocytes. Neuronal glutamate released during neuronal activity was postulated to enhance this β-oxidation and lipid detoxification by binding to N-methyl-D-aspartate (NMDA) receptors on the astrocytes.

While these findings underscore the importance of neuron-to-astrocyte lipid transfer in protecting neurons from lipid toxicity, it has also been revealed that lipid fluxes between these cells follow a circadian rhythm[163]. During wakefulness, mitochondrial energetic activity is heightened in neurons[164], resulting in the production of ROS and formation of peroxidated lipids. These peroxidated lipids are shuttled by apolipoproteins to neighboring glia, where they were sequestered into lipid droplets, thereby effectively reducing neuronal ROS levels. During sleep, the peroxidated lipids contained within the glial lipid droplets were catabolized, removing toxic radicals and producing energy to

support future neuronal activities. All in all, these studies indicate that stressed and (hyper)active neurons protect themselves from ROS and lipid peroxidation by transferring toxic lipids to glial cells.

Alongside these protective functions, intercellular lipid coupling between astrocytes and neurons can lead to cytodegeneration. For example, astrocytes primed with inflammatory mediators released by activated microglia — interleukin 1α (IL1α), tumor necrosis factor (TNF), and complement component 1q (C1QA) — increase the loading of APOE and APOJ lipoproteins with toxic long-chain SFAs (**Fig. 2**)[120]. Hindering the synthesis of these long-chain SFAs by selectively knocking out *Elovl1* in astrocytes mitigates astrocyte-mediated toxicity. The release of these toxic long chain SFAs by reactive astrocytes is likely to contribute to the cytotoxic effects of IL1α, TNF, and C1QA on ganglion cells following retinal injury[165,166]. Why reactive astrocytes upregulate the loading of saturated lipids on APOE and APOJ lipoproteins, and to what extent these FAs are differentially trafficked by reactive astrocytes that express divergent APOE isoforms, remains unclear. With respect to the latter, isoform- and cell-state-specific differences in the lipidation of APOE in astrocytes have been reported[167]. Specifically, astrocytes chronically exposed to FAs and having excess lipid droplets produce TAG-rich APOE particles, a process that is boosted by the APOE4 variant[167]. Whether there is a differential loading of APOE2, APOE3, and APOE4 with toxic long-chain SFA in reactive astrocytes, however, remains to be determined.

**[H2] Glia-glia lipid transfer**

Oligodendrocytes are the myelinating cells of the CNS, enveloping axons with layered, lipid-rich membranes that enable rapid saltatory axonal conduction[168]. Cholesterol is a critical component of myelin membranes and thus adequate levels of cholesterol are essential for developmental myelination and the regeneration of myelin in response to pathological demyelination. Since peripheral cholesterol entry into the CNS is restricted by the BBB, oligodendrocytes and OPCs have adapted to synthesize their own cholesterol (**Fig. 2**)[12,169]. Disruptions in this process can result in

oligodendrocyte apoptosis, developmental hypomyelination and impaired remyelination following demyelinating events[12,36,170,171]. Despite FA being able to cross the BBB, oligodendrocytes also depend on de novo FA synthesis for developmental myelination and remyelination[50], which is consistent with FAs being enriched in myelin and contributing to its structural integrity[172]. This discrepancy may reflect the fact that SFA and MUFAs, which are major products of de novo lipid synthesis, are less efficient at traversing the BBB (**Box 2**). In addition to the cell-autonomous synthesis of cholesterol and FAs by oligodendrocytes and OPCs, intercellular lipid transfer has recently been shown to be essential for providing oligodendrocytes with lipids.

Microglia and subsets of CNS-infiltrating macrophages are increasingly being recognized for their role in meeting the demand for cholesterol by oligodendrocytes, particularly following pathological demyelination. These cells remove damaged myelin and myelin debris via phagocytosis and subsequently process and transfer myelin-derived lipids to supply oligodendroglia with the cholesterol necessary for myelin membrane formation (**Fig. 2**)[173]. Mechanistically, upon receptor-mediated phagocytosis, the lysosomal degradation and intracellular processing of myelin by these cells leads to formation of oxysterols that activate cholesterol-sensing LXRs[173-175]. Recent work has shown that these receptors can also be activated by metabolites such as desmosterol that arise as a result of increased cholesterol synthesis following demyelination[171]. A similar feedback loop involving lipid-loaded macrophages, LXRs, and desmosterol is observed following low density lipoprotein (LDL) internalization in atherosclerosis[176]. Regardless of the mode of activation, LXR activation induces an inflammatory and metabolic phenotype in macrophages and microglia that supports tissue regeneration[177]. LXR activation also enhances the abundance of ATP-binding cassette transporter A1 ABCA1, promoting apolipoprotein lipid loading and providing a readily available pool of cholesterol for oligodendroglia to generate new myelin sheaths following demyelination[25].

The aforementioned studies underscore the essential role of the efficient remodeling and intercellular transfer of myelin-derived cholesterol by phagocytes in fueling remyelination in CNS

disorders. However, studies have shown that, at progressive stages of demyelinating diseases and during aging, LXR signaling becomes impaired and lipid remodeling and transfer become suboptimal in the CNS[19,89]. Over time, the sustained intracellular accumulation of myelin-derived lipids perturbs the metabolic phenotype of macrophages and microglia[19,54,95,106]. For example, macrophages and microglia containing abundant myelin-derived lipids exhibit a reduced capacity for lipid droplet catabolism through lipophagy and lipolysis[95,106]. In addition, the intracellular accumulation of myelin-derived lipids leads to elevated expression of enzymes involved in FA desaturation and elongation (SCD1 and ELOVL6 in particular), resulting in the generation of ABCA1-destabilizing FAs and impaired lipid loading into lipoproteins[19,54]. This disturbed metabolism and transfer of myelin-derived lipids contributes to the induction of a highly inflammatory macrophage and microglia phenotype that impairs OPC maturation and remyelination[19,54,106]. Similarly, aging affects the phenotype of myelin-containing microglia in the CNS[89,178,179], and is a major impediment to adequate remyelination[180]. Aging compromises the capacity of microglia to clear damaged myelin debris, which is a necessary prerequisite for remyelination[181]. Aged myelin-containing microglia further demonstrate increased lipid droplet formation and elevated ROS production[86,178,179]. Finally, aged microglia exhibit an impaired ability to recycle large amounts of intracellular cholesterol-rich myelin debris and display reduced LXR activation, leading to lysosomal cholesterol accumulation[89]. The accumulation of lysosomal cholesterol results in the formation of cholesterol crystals, which induces lysosomal rupture and the activation of the NLRP3 inflammasome, thereby impairing remyelination. To address disruptions in lipid remodeling and transfer in myelin-containing phagocytes, a recent used an apolipoprotein A1 (APOA1) mimetic peptide to promote the stabilization and efflux capacity of ABCA1, which was effective in restoring both the intracellular processing of myelin-derived lipids in microglia and the transfer of these lipids to oligodendrocytes[99]. It is important to note that dietary cholesterol can also enhance remyelination[182], potentially bypassing disturbances in lipid remodeling and transfer by increasing extracellular cholesterol availability in the CNS. However, given cholesterol's inability to cross the BBB, future research will be needed to explore whether dietary cholesterol

supplementation can offer beneficial effects in CNS disorders at disease stages in which the BBB retains or regains its integrity. Collectively, these studies indicate that disrupted remodeling and efflux of myelin-derived lipids in phagocytes can contribute to the failure of remyelination.

The transfer of lipids between astrocytes and oligodendrocytes also plays an essential role in myelination and remyelination. While deficiency of *Scap* in oligodendrocytes impairs myelination only in young mice, astrocyte-specific deficiency of *Scap* leads to persistent hypomyelination[183]. Interestingly, this hypomyelination could be rescued by providing a diet enriched in cholesterol and oleic acid. These findings underscore the important role of astrocyte-oligodendrocyte lipid transfer in the formation and maintenance of myelin, especially during adulthood, and suggest that dietary interventions hold promise as therapeutic strategies to correct for disturbances in the intercellular transfer of lipids in the CNS. Astrocytic lipid transfer to oligodendrocytes also promotes remyelination in models of toxin-induced demyelination[184]. It has been demonstrated that remyelination is characterized by increased cholesterol biosynthesis in astrocytes and elevated ABCA1-mediated cholesterol transfer to oligodendrocytes. These changes inversely correlated with the activity of nuclear factor erythroid 2–related factor 2 (NRF2), a key regulator of cellular oxidative stress responses (**Fig. 2**). The molecular mechanisms underlying the regulation of cholesterol biosynthesis and efflux by NRF2 have yet to be elucidated. A similar inverse relationship between cholesterol metabolism and NRF2 activity was previously reported in the liver of *Nrf2*$^{-/-}$ mice fed a high-fat diet (HFD)[185]. Given the low abundance and activity of NRF2 in neurons[186], it is tempting to speculate that a feedback mechanism in which low NRF2 activity enhances cholesterol efflux may also facilitate the ABCA1-mediated clearance of toxic peroxidated lipids from neurons to astrocytes[157,159,164].

Overall, proper glia-glia lipid transfer has an essential role in developmental myelination, myelin maintenance, and remyelination. Interestingly, there appears to be a divergence in how brain and spinal cord oligodendroglia acquire cholesterol, with spinal cord oligodendroglia relying more on de

novo synthesis and brain oligodendroglia on extracellular cholesterol uptake[170]. This distinction warrants further investigation, as it may offer valuable insights into the therapeutic potential of modulators targeting lipid disturbances in brain and spinal cord pathologies.

**[H2] Lipid transfer by extracellular vesicles**

EVs, including exosomes and microvesicles, are small, membrane-bound vesicles that are released from cells and facilitate intercellular communication. Alongside proteins and miRNAs, EVs transfer lipids between cells[187]. Several studies have demonstrated that the transfer of EV-associated lipids is essential for maintaining CNS homeostasis by influencing oligodendroglia physiology. Specifically, recent research showed that EVs secreted by pro-regenerative microglia enhance OPC migration and remyelination in a lysolecithin-induced demyelination model through the intercellular transfer of sphingosine-1-phosphate[188]. Supporting the importance of EV-associated lipids in remyelination, a study by Vanherle *et al.* found that EVs released by IL4-exposed macrophages enhance remyelination ex vivo and in vivo by promoting the differentiation of OPCs (**Fig. 2**)[18]. Guided by lipidomic analysis and by experiments utilizing cholesterol depletion and enrichment strategies, the authors attributed the pro-regenerative effects of EVs to elevated cholesterol levels. Mechanistically, EV-associated cholesterol was found to promote OPC differentiation primarily by supplying cholesterol to the oligodendrocyte membrane through direct membrane fusion[18]. By contrast, a study by Lombardi *et al*. found that EVs from IL-4-exposed macrophages do not facilitate OPC maturation, while those from macrophages exposed to inflammatory cytokines hinder OPC maturation[189]; however, the lipid fraction of EVs isolated from inflammatory macrophages did promote OPC maturation, likely through pro-regenerative endocannabinoids such as anandamide and 2-arachidonoylglycerol present within these EVs. This suggests that other detrimental factors present in EVs can outweigh the pro-regenerative impact of endocannabinoids. The divergent outcomes of these studies may stem from differences in the experimental systems used (rat vs. mouse), the duration of OPC exposure to EVs (2 days vs. 6 days), and the EV isolation methods used[18,189]. In light of the latter, Vanherle *et al.* incorporated an additional purification step to minimize potential contaminants[190].

The essential role of EVs as transport vehicles for lipid transfer is also evident in neurodegenerative disorders such as AD and PD. In an animal model for AD, Aβ aggregation was found to promote the incorporation of pro-apoptotic ceramide classes into EVs secreted by astrocytes[191]. Furthermore, neuron-derived EVs have been shown to contain glycosphingolipids that facilitate the targeting of Aβ to microglia for clearance[192-195]. In PD patients, EVs purified from cerebrospinal fluid and frontal cortex are also heavily loaded with ceramides and neurodegeneration-linked proteins, including α-syn[196]. In vitro studies confirmed that these EVs constitute a "pathological package" capable of inducing aggregation of α-syn[196]. Similarly, the EV-associated gangliosides GM1 and GM3 have been identified as key factors in promoting α-syn oligomerization[197]. Overall, these studies point towards EVs playing an important role in the transfer and distribution of lipids in the CNS. By transferring lipids between cells, EVs help to maintain the complex lipid landscape essential for glial and neuronal function. However, the relative importance of EVs in driving intercellular lipid transfer in the healthy and diseased CNS, compared to lipoproteins and the poorly understood tunneling nanotubes (**Box 3**), remains to be determined.

### [H1] External influences on lipid metabolism

Emerging evidence highlights the influence of environmental factors, diet, and lifestyle on CNS lipid metabolism. Specifically, avoiding a Western diet **[G]**, engaging in regular physical activity, managing stress and sleep patterns, and minimizing exposure to harmful substances are pivotal for maintaining effective lipid remodeling and intercellular transfer in the CNS.

#### [H2] Environmental factors

Environmental factors, including pollutants, climate, and pathogens, are increasingly acknowledged to impact lipid remodeling in the CNS. Pollutants, including micro- and nanoplastics as well as air contaminants, can cross the BBB, induce lipid peroxidation, and cause mitochondrial dysfunction and lysosomal disruption in glial cells and neurons[198-200]. With regard to climate, a recent preprint has reported that cold exposure (4 °C; 4–6 hours) enhances neuronal activity-dependent lipid metabolic

processes in the brain, including lipid peroxidation, lipid droplet formation, and lipolysis[201], in agreement with its reported effects on lipid metabolism in adipose and skeletal tissues[202-206]. By contrast, a reduction in ambient temperature (17 °C; 5 weeks) was found to reduce obesity-induced lipid peroxidation in the hypothalamus of mice, which was associated with a decreased inflammatory burden[207]. This discrepancy may reflect differences between acute, severe cold exposure and prolonged, mild cold exposure. Finally, a recent study found that the Zika virus modulates neuronal lipid metabolism to favor its replication and survival, leading to significant lipid droplet accumulation in human neuroblastoma cells and neural stem cells (NSCs) in vitro[208]. Consistent with this, astrocytic lipid droplet accumulation was observed following exposure to Zika virus, Herpes Simplex virus 1, and dengue virus in vitro, with the latter also increasing lipid droplet accumulation within the brain of mice[209].

**[H2] Diet**

The typical Western diet, rich in SFAs, trans FAs (unsaturated FAs with at least one double bond in the less common trans configuration that increases rigidity), ω-6 PUFAs, sugars, and cholesterol, is increasingly being linked to CNS pathologies[210]. Dietary lipids can influence CNS-resident cell physiology either directly or indirectly through their effects on the microbiome, vasculature, and adipose tissue[21,210,211], which complicates the interpretation of studies. Despite these complexities, a few studies have demonstrated that a Western diet affects lipid remodeling and intercellular lipid transfer in the CNS. For example, Bosch-Queralt *et al.* showed that a Western Diet triggers a dysfunctional metabolic response associated with impaired myelin debris clearance in microglia, thereby attenuating lesion recovery in a mouse model of demyelination[212]. Mechanistically, this was attributed to a reduced activation of LXR-regulated genes encoding proteins involved in cholesterol efflux, including *Apoe*, *Abca1*, and *Abcg1*, which perturbed microglial processing and efflux of myelin and cholesterol. By contrast, in humanized mice homozygous for APOE2, APOE3, and APOE4, a Western diet was found to increase total brain APOE levels in an allele-dependent fashion, with the most significant increase observed in APOE2[213]. The discrepancy in the effects of a Western diet on

APOE abundance could arise from the existence of an already perturbed foamy microglia metabolic phenotype during demyelination[19,89]. Alternatively, it may have arisen because Bosch-Queralt *et al*. compared APOE levels only across different lesion stages, without assessing levels at baseline prior to toxin-induced demyelination.

In addition to affecting intercellular lipid fluxes in the CNS, studies have shown that exposing mice to a high fat diet (HFD), a subtype of the Western diet that is enriched in SFAs and unsaturated fatty acids (UFAs) but lacks substantial amounts of cholesterol and sugars, disturbs lipid droplet breakdown by reducing lipophagy[214,215]. Hippocampal microglia in a mouse model of type 2 diabetes induced by an HFD exhibit lipid droplet accumulation and significant impairment of lipophagy[214]. Lipid droplets were found to colocalize with and hinder the degradation of TREM1, thereby perpetuating neuroinflammation and impairing cognitive function. Interestingly, another study found that chronic HFD consumption enhances lipid droplet accumulation and impairs mito- and lipophagy in the hypothalamus of male but not female mice[215]. This suggests a sexually dimorphic response to chronic HFD exposure, with females exhibiting protection against the adverse metabolic effects of the diet. An HFD is further associated with increased brain ROS levels and lipid peroxidation (reviewed in [216]), and disruptions in the quantity and quality of (lyso)phospholipids during HFD feeding[217], reflecting alterations in the Kennedy pathway and Lands cycle. Collectively, these findings highlight the detrimental effects of Western diets on lipid remodeling and intercellular transfer within the CNS. Establishing causality between these diet-induced alterations in lipid metabolism and CNS pathology in neurodegenerative disorders, while considering sex differences, will be an important goal of future research. Comparing these effects to those of intermittent fasting, which exerts opposing influences on these processes (reviewed in [218]), would also be of interest.

**[H2] Lifestyle**

Disruptions in circadian rhythm are increasingly linked to CNS pathologies, including AD and PD[219], but the molecular drivers remain poorly understood. Recent studies have shown that the circadian clock

regulates lipid remodeling and intercellular transfer in the CNS[163,220,221]. The transfer of peroxidated lipids from hyperactive neurons to astrocytes, along with their subsequent storage and breakdown within astrocytes, follows a circadian pattern and is essential to retain CNS homeostasis[163]. Mirroring these findings, most apolipoprotein genes show rhythmic expression in the CNS (reviewed in [220]). Hence, it is tempting to speculate that disruptions in sleep patterns or disease-related alterations in circadian rhythms could contribute to lipid dyshomeostasis in CNS disorders. Regarding the latter, a recent preprint has reported that, while showing rhythmicity in controls, *Srebf1*, the gene encoding SREBP1, which is involved in lipid synthesis, loses its rhythmicity in an experimental model of AD[221]. The extent to which intracellular accumulation of myelin or other pathogenic protein aggregates disrupts the rhythmicity of lipid metabolism, leading to glial and neuronal dysfunction, remains to be determined.

Alongside disturbances in circadian rhythms, some studies suggest that acute and chronic physiological stress are associated with alterations in lipid remodeling and intercellular transfer in the CNS. Chronic physiological stress increases CNS lipid peroxidation, which can be mitigated by treatment with non-selective reactive nitrogen species (RNS) and ROS inhibitors[222]. By using a multi-omics approach, a recent study found that acute physiological stress correlates with an increase in the levels of lysophospholipids lacking acyl chains at the sn-2 position, indicative of increased PLA2 activity, and increased levels of eicosanoid and endocannabinoids in the mouse brain[223]. Similarly, single-nuclei RNA sequencing demonstrated that acute stress induces rapid and marked differences in the expression of lipid transfer and remodeling genes in astrocytes, microglia, neurons, or oligodendrocytes, including but not limited to *Apoe*, *Abca1*, *Plin2*, *Nrf2*, and diverse lipases and acyltransferases[224]. The relevance of these metabolic changes in driving disease pathology in neurodegenerative disorders remains unclear, but is highly pertinent in an increasingly stressed society.

## [H1] Conclusions

In recent years, it has become clear that lipid metabolism, remodeling and intercellular transfer are essential for maintaining or restoring lipid homeostasis in the CNS, with substantial evidence highlighting the key roles of lipid synthesis, lipid droplet biogenesis and breakdown, lipid oxidation, phospholipid metabolism, lipoprotein-mediated lipid transfer, and EVs. Importantly, various genetic factors (such as variants in *APOE*, *TREM2*, and *PLA2G6*), environmental influences (such as stress, circadian rhythm, diet, climate, and pathogens), and disease-associated pathological hallmarks (such as ROS, inflammation, and cellular accumulation of Aβ, α-synuclein, and myelin debris) have been identified as key drivers of dysfunction in these metabolic pathways.

In the upcoming years, novel lipidomics techniques will allow researchers to further unravel the molecular blueprints of disturbed lipid metabolism in the CNS. Tracer lipidomics using isotope-labeled lipid metabolites could provide precise analyses of lipid flux and transfer dynamics in the healthy and diseased CNS[225]. Combined with mass spectrometry imaging and Raman microscopy, researchers could further obtain spatial information on changes in the lipidome and lipid transfer on a subcellular level[226-230]. Such experiments could explain why certain lipid types (such as long-chain SFAs, lysophospholipids, and cholesterol) that are essential membrane constituents and cell signaling molecules in the CNS become toxic under specific conditions. While this may stem from supra-homeostatic or atypical lipid accumulations in organelles or cells — such as neurons and foamy microglia — that lack the necessary machinery (or progressively become less able) to properly metabolize or store them, more complex processes may also be involved. Furthermore, these novel techniques could enable the detailed assessment of whether the lipid metabolism, remodeling, and intercellular transfer mechanisms discussed in this review are differentially active in neurons and glial cells during homeostasis and disease.

Overall, while further in-depth lipidomic studies are needed, it is clear that lipid remodeling and intercellular transfer are promising therapeutic targets for restoring CNS homeostasis in neurological disorders such as MS, AD, PD, and HD.

## 5. References


1 Yoon, J. H. *et al.* Brain lipidomics: From functional landscape to clinical significance. *Sci Adv* **8**, eadc9317, doi:10.1126/sciadv.adc9317 (2022).

2 Sastry, P. S. Lipids of nervous tissue: composition and metabolism. *Prog Lipid Res* **24**, 69-176, doi:10.1016/0163-7827(85)90011-6 (1985).

3 van Echten-Deckert, G. The role of sphingosine 1-phosphate metabolism in brain health and disease. *Pharmacol Ther* **244**, 108381, doi:10.1016/j.pharmthera.2023.108381 (2023).

4 Baggelaar, M. P., Maccarrone, M. & van der Stelt, M. 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. *Prog Lipid Res* **71**, 1-17, doi:10.1016/j.plipres.2018.05.002 (2018).

5 Valles, A. S. & Barrantes, F. J. The synaptic lipidome in health and disease. *Biochim Biophys Acta Biomembr* **1864**, 184033, doi:10.1016/j.bbamem.2022.184033 (2022).

6 Osetrova, M. *et al.* Lipidome atlas of the adult human brain. *Nat Commun* **15**, 4455, doi:10.1038/s41467-024-48734-y (2024).

7 Tracey, T. J., Kirk, S. E., Steyn, F. J. & Ngo, S. T. The role of lipids in the central nervous system and their pathological implications in amyotrophic lateral sclerosis. *Semin Cell Dev Biol* **112**, 69-81, doi:10.1016/j.semcdb.2020.08.012 (2021).

8 Jiménez-Rojo, N. & Riezman, H. On the road to unraveling the molecular functions of ether lipids. *FEBS Lett* **593**, 2378-2389, doi:10.1002/1873-3468.13465 (2019).

9 van Meer, G., Voelker, D. R. & Feigenson, G. W. Membrane lipids: where they are and how they behave. *Nat Rev Mol Cell Biol* **9**, 112-124, doi:10.1038/nrm2330 (2008).

10 Zhang, W., Trible, R. P. & Samelson, L. E. LAT palmitoylation: its essential role in membrane microdomain targeting and tyrosine phosphorylation during T cell activation. *Immunity* **9**, 239-246, doi:10.1016/s1074-7613(00)80606-8 (1998).

11 Montaner, A. *et al.* Specific Phospholipids Regulate the Acquisition of Neuronal and Astroglial Identities in Post-Mitotic Cells. *Sci Rep* **8**, 460, doi:10.1038/s41598-017-18700-4 (2018).

12 Saher, G. *et al.* High cholesterol level is essential for myelin membrane growth. *Nat Neurosci* **8**, 468-475, doi:10.1038/nn1426 (2005).

13 Coelho, R. P., Saini, H. S. & Sato-Bigbee, C. Sphingosine-1-phosphate and oligodendrocytes: from cell development to the treatment of multiple sclerosis. *Prostaglandins Other Lipid Mediat* **91**, 139-144, doi:10.1016/j.prostaglandins.2009.04.002 (2010).

14 Walther, T. C. & Farese, R. V., Jr. The life of lipid droplets. *Biochim Biophys Acta* **1791**, 459-466, doi:10.1016/j.bbalip.2008.10.009 (2009).

15 Arendt, K. L. *et al.* PIP3 controls synaptic function by maintaining AMPA receptor clustering at the postsynaptic membrane. *Nat Neurosci* **13**, 36-44, doi:10.1038/nn.2462 (2010).

16 Jiang, X. *et al.* Simvastatin blocks blood-brain barrier disruptions induced by elevated cholesterol both in vivo and in vitro. *Int J Alzheimers Dis* **2012**, 109324, doi:10.1155/2012/109324 (2012).

17 Mehdi, S. M. A. *et al.* Depression and cognition are associated with lipid dysregulation in both a multigenerational study of depression and the National Health and Nutrition Examination Survey. *Transl Psychiatry* **14**, 142, doi:10.1038/s41398-024-02847-6 (2024).

18 Vanherle, S. *et al.* Extracellular vesicle-associated cholesterol supports the regenerative functions of macrophages in the brain. *J Extracell Vesicles* **12**, e12394, doi:10.1002/jev2.12394 (2023).

19 Bogie, J. F. J. *et al.* Stearoyl-CoA desaturase-1 impairs the reparative properties of macrophages and microglia in the brain. *J Exp Med* **217**, doi:10.1084/jem.20191660 (2020).

20 Wu, J. *et al.* Nonvesicular lipid transfer drives myelin growth in the central nervous system. *Nat Commun* **15**, 9756, doi:10.1038/s41467-024-53511-y (2024).
21 Bogie, J. F. J., Haidar, M., Kooij, G. & Hendriks, J. J. A. Fatty acid metabolism in the progression and resolution of CNS disorders. *Adv Drug Deliv Rev* **159**, 198-213, doi:10.1016/j.addr.2020.01.004 (2020).
22 Valenza, M., Birolini, G. & Cattaneo, E. The translational potential of cholesterol-based therapies for neurological disease. *Nat Rev Neurol* **19**, 583-598, doi:10.1038/s41582-023-00864-5 (2023).
23 Dietschy, J. M. Central nervous system: cholesterol turnover, brain development and neurodegeneration. *Biol Chem* **390**, 287-293, doi:10.1515/bc.2009.035 (2009).
24 Dietschy, J. M. & Turley, S. D. Thematic review series: brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *J Lipid Res* **45**, 1375-1397, doi:10.1194/jlr.R400004-JLR200 (2004).
25 Berghoff, S. A., Spieth, L. & Saher, G. Local cholesterol metabolism orchestrates remyelination. *Trends Neurosci* **45**, 272-283, doi:10.1016/j.tins.2022.01.001 (2022).
26 Orth, M. & Bellosta, S. Cholesterol: its regulation and role in central nervous system disorders. *Cholesterol* **2012**, 292598, doi:10.1155/2012/292598 (2012).
27 Quan, G., Xie, C., Dietschy, J. M. & Turley, S. D. Ontogenesis and regulation of cholesterol metabolism in the central nervous system of the mouse. *Brain research. Developmental brain research* **146**, 87-98, doi:10.1016/j.devbrainres.2003.09.015 (2003).
28 Morell, P. & Jurevics, H. Origin of cholesterol in myelin. *Neurochemical research* **21**, 463-470, doi:10.1007/BF02527711 (1996).
29 Andersson, M., Elmberger, P. G., Edlund, C., Kristensson, K. & Dallner, G. Rates of cholesterol, ubiquinone, dolichol and dolichyl-P biosynthesis in rat brain slices. *FEBS letters* **269**, 15-18, doi:10.1016/0014-5793(90)81107-y (1990).
30 Wang, H. & Eckel, R. H. What are lipoproteins doing in the brain? *Trends Endocrinol Metab* **25**, 8-14, doi:10.1016/j.tem.2013.10.003 (2014).
31 Valenza, M. *et al.* Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. *J Neurosci* **25**, 9932-9939, doi:10.1523/jneurosci.3355-05.2005 (2005).
32 Thelen, K. M., Falkai, P., Bayer, T. A. & Lütjohann, D. Cholesterol synthesis rate in human hippocampus declines with aging. *Neurosci Lett* **403**, 15-19, doi:10.1016/j.neulet.2006.04.034 (2006).
33 Stommel, A., Berlet, H. H. & Debuch, H. Buoyant density and lipid composition of purified myelin of aging human brain. *Mech Ageing Dev* **48**, 1-14, doi:10.1016/0047-6374(89)90021-3 (1989).
34 Boisvert, M. M., Erikson, G. A., Shokhirev, M. N. & Allen, N. J. The Aging Astrocyte Transcriptome from Multiple Regions of the Mouse Brain. *Cell Rep* **22**, 269-285, doi:10.1016/j.celrep.2017.12.039 (2018).
35 Habib, N. *et al.* Disease-associated astrocytes in Alzheimer's disease and aging. *Nat Neurosci* **23**, 701-706, doi:10.1038/s41593-020-0624-8 (2020).
36 Miron, V. E. *et al.* Statin therapy inhibits remyelination in the central nervous system. *Am J Pathol* **174**, 1880-1890, doi:10.2353/ajpath.2009.080947 (2009).
37 Leitmeyer, K. *et al.* Simvastatin Results in a Dose-Dependent Toxic Effect on Spiral Ganglion Neurons in an In Vitro Organotypic Culture Assay. *Biomed Res Int* **2016**, 3580359, doi:10.1155/2016/3580359 (2016).
38 Schulz, J. G. *et al.* HMG-CoA reductase inhibition causes neurite loss by interfering with geranylgeranylpyrophosphate synthesis. *J Neurochem* **89**, 24-32, doi:10.1046/j.1471-4159.2003.02305.x (2004).
39 Wood, W. G., Eckert, G. P., Igbavboa, U. & Muller, W. E. Statins and neuroprotection: a prescription to move the field forward. *Ann N Y Acad Sci* **1199**, 69-76, doi:10.1111/j.1749-6632.2009.05359.x (2010).

40 Wang, M., Wang, J., Liu, M. & Chen, G. Fluvastatin protects neuronal cells from hydrogen peroxide-induced toxicity with decreasing oxidative damage and increasing PI3K/Akt/mTOR signalling. *J Pharm Pharmacol* **73**, 515-521, doi:10.1093/jpp/rgaa058 (2021).
41 Ekladious, S. T. & El Sayed, N. S. Effect of pioglitazone and simvastatin in lipopolysaccharide-induced amyloidogenesis and cognitive impairment in mice: possible role of glutamatergic pathway and oxidative stress. *Behav Pharmacol* **30**, 5-15, doi:10.1097/FBP.0000000000000407 (2019).
42 Miron, V. E. *et al.* Simvastatin regulates oligodendroglial process dynamics and survival. *Glia* **55**, 130-143, doi:10.1002/glia.20441 (2007).
43 Refolo, L. M. *et al.* A cholesterol-lowering drug reduces beta-amyloid pathology in a transgenic mouse model of Alzheimer's disease. *Neurobiol Dis* **8**, 890-899, doi:10.1006/nbdi.2001.0422 (2001).
44 Simons, M. *et al.* Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. *Proc Natl Acad Sci U S A* **95**, 6460-6464, doi:10.1073/pnas.95.11.6460 (1998).
45 Wang, H. *et al.* Regulation of beta-amyloid production in neurons by astrocyte-derived cholesterol. *Proc Natl Acad Sci U S A* **118**, doi:10.1073/pnas.2102191118 (2021).
46 Marquer, C. *et al.* Increasing membrane cholesterol of neurons in culture recapitulates Alzheimer's disease early phenotypes. *Mol Neurodegener* **9**, 60, doi:10.1186/1750-1326-9-60 (2014).
47 van der Kant, R., Goldstein, L. S. B. & Ossenkoppele, R. Amyloid-beta-independent regulators of tau pathology in Alzheimer disease. *Nat Rev Neurosci* **21**, 21-35, doi:10.1038/s41583-019-0240-3 (2020).
48 Wang, H. *et al.* Biphasic effects of statins on neuron cell functions under oxygen-glucose deprivation and normal culturing conditions via different mechanisms. *Pharmacol Res Perspect* **10**, e01001, doi:10.1002/prp2.1001 (2022).
49 Garcia Corrales, A. V., Haidar, M., Bogie, J. F. J. & Hendriks, J. J. A. Fatty Acid Synthesis in Glial Cells of the CNS. *Int J Mol Sci* **22**, doi:10.3390/ijms22158159 (2021).
50 Dimas, P. *et al.* CNS myelination and remyelination depend on fatty acid synthesis by oligodendrocytes. *Elife* **8**, doi:10.7554/eLife.44702 (2019).
51 Lebrun-Julien, F. *et al.* Balanced mTORC1 activity in oligodendrocytes is required for accurate CNS myelination. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **34**, 8432-8448, doi:10.1523/JNEUROSCI.1105-14.2014 (2014).
52 Knobloch, M. *et al.* Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. *Nature* **493**, 226-230, doi:10.1038/nature11689 (2013).
53 Ziegler, A. B. *et al.* Cell-Autonomous Control of Neuronal Dendrite Expansion via the Fatty Acid Synthesis Regulator SREBP. *Cell Rep* **21**, 3346-3353, doi:10.1016/j.celrep.2017.11.069 (2017).
54 Garcia Corrales, A. V. *et al.* Fatty acid elongation by ELOVL6 hampers remyelination by promoting inflammatory foam cell formation during demyelination. *Proc Natl Acad Sci U S A* **120**, e2301030120, doi:10.1073/pnas.2301030120 (2023).
55 Grajchen, E. *et al.* Fatty acid desaturation by stearoyl-CoA desaturase-1 controls regulatory T cell differentiation and autoimmunity. *Cell Mol Immunol*, doi:10.1038/s41423-023-01011-2 (2023).
56 Hamilton, L. K. *et al.* Aberrant Lipid Metabolism in the Forebrain Niche Suppresses Adult Neural Stem Cell Proliferation in an Animal Model of Alzheimer's Disease. *Cell Stem Cell* **17**, 397-411, doi:10.1016/j.stem.2015.08.001 (2015).
57 Fanning, S. *et al.* Lipidomic Analysis of alpha-Synuclein Neurotoxicity Identifies Stearoyl CoA Desaturase as a Target for Parkinson Treatment. *Mol Cell* **73**, 1001-1014 e1008, doi:10.1016/j.molcel.2018.11.028 (2019).
58 Loix, M. *et al.* Stearoyl-CoA desaturase-1: a potential therapeutic target for neurological disorders. *Mol Neurodegener* **19**, 85, doi:10.1186/s13024-024-00778-w (2024).

59 Bazinet, R. P. & Laye, S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat Rev Neurosci* **15**, 771-785, doi:10.1038/nrn3820 (2014).
60 Brennan, E., Kantharidis, P., Cooper, M. E. & Godson, C. Pro-resolving lipid mediators: regulators of inflammation, metabolism and kidney function. *Nat Rev Nephrol* **17**, 725-739, doi:10.1038/s41581-021-00454-y (2021).
61 Serhan, C. N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* **510**, 92-101, doi:10.1038/nature13479 (2014).
62 Dunn, H. C. *et al.* Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model. *J Alzheimers Dis* **43**, 893-903, doi:10.3233/JAD-141335 (2015).
63 Derada Troletti, C. *et al.* Pro-resolving lipid mediator lipoxin A(4) attenuates neuro-inflammation by modulating T cell responses and modifies the spinal cord lipidome. *Cell Rep* **35**, 109201, doi:10.1016/j.celrep.2021.109201 (2021).
64 Kooij, G. *et al.* Specialized pro-resolving lipid mediators are differentially altered in peripheral blood of patients with multiple sclerosis and attenuate monocyte and blood-brain barrier dysfunction. *Haematologica* **105**, 2056-2070, doi:10.3324/haematol.2019.219519 (2020).
65 Duffney, P. F. *et al.* Key roles for lipid mediators in the adaptive immune response. *J Clin Invest* **128**, 2724-2731, doi:10.1172/JCI97951 (2018).
66 Jiang, X., Stockwell, B. R. & Conrad, M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol* **22**, 266-282, doi:10.1038/s41580-020-00324-8 (2021).
67 Dong, Y. *et al.* Oxidized phosphatidylcholines found in multiple sclerosis lesions mediate neurodegeneration and are neutralized by microglia. *Nat Neurosci* **24**, 489-503, doi:10.1038/s41593-021-00801-z (2021).
68 Dong, Y. & Yong, V. W. Oxidized phospholipids as novel mediators of neurodegeneration. *Trends Neurosci* **45**, 419-429, doi:10.1016/j.tins.2022.03.002 (2022).
69 Bjorkhem, I. *et al.* From brain to bile. Evidence that conjugation and omega-hydroxylation are important for elimination of 24S-hydroxycholesterol (cerebrosterol) in humans. *J Biol Chem* **276**, 37004-37010, doi:10.1074/jbc.M103828200 (2001).
70 Bjorkhem, I. & Meaney, S. Brain cholesterol: long secret life behind a barrier. *Arterioscler Thromb Vasc Biol* **24**, 806-815, doi:10.1161/01.ATV.0000120374.59826.1b (2004).
71 Brown, J., 3rd *et al.* Differential expression of cholesterol hydroxylases in Alzheimer's disease. *J Biol Chem* **279**, 34674-34681, doi:10.1074/jbc.M402324200 (2004).
72 Abildayeva, K. *et al.* 24(S)-hydroxycholesterol participates in a liver X receptor-controlled pathway in astrocytes that regulates apolipoprotein E-mediated cholesterol efflux. *J Biol Chem* **281**, 12799-12808, doi:10.1074/jbc.M601019200 (2006).
73 Testa, G. *et al.* Changes in brain oxysterols at different stages of Alzheimer's disease: Their involvement in neuroinflammation. *Redox Biol* **10**, 24-33, doi:10.1016/j.redox.2016.09.001 (2016).
74 Gamba, P. *et al.* Up-regulation of beta-amyloidogenesis in neuron-like human cells by both 24- and 27-hydroxycholesterol: protective effect of N-acetyl-cysteine. *Aging Cell* **13**, 561-572, doi:10.1111/acel.12206 (2014).
75 Marwarha, G., Dasari, B., Prasanthi, J. R., Schommer, J. & Ghribi, O. Leptin reduces the accumulation of Abeta and phosphorylated tau induced by 27-hydroxycholesterol in rabbit organotypic slices. *J Alzheimers Dis* **19**, 1007-1019, doi:10.3233/JAD-2010-1298 (2010).
76 Wang, Y. *et al.* 27-Hydroxycholesterol-Induced Dysregulation of Cholesterol Metabolism Impairs Learning and Memory Ability in ApoE epsilon4 Transgenic Mice. *Int J Mol Sci* **23**, doi:10.3390/ijms231911639 (2022).
77 Chen, S. *et al.* 27-Hydroxycholesterol Contributes to Lysosomal Membrane Permeabilization-Mediated Pyroptosis in Co-cultured SH-SY5Y Cells and C6 Cells. *Front Mol Neurosci* **12**, 14, doi:10.3389/fnmol.2019.00014 (2019).

78 Merino-Serrais, P. *et al.* 27-Hydroxycholesterol Induces Aberrant Morphology and Synaptic Dysfunction in Hippocampal Neurons. *Cereb Cortex* **29**, 429-446, doi:10.1093/cercor/bhy274 (2019).
79 Loera-Valencia, R. *et al.* High levels of 27-hydroxycholesterol results in synaptic plasticity alterations in the hippocampus. *Sci Rep* **11**, 3736, doi:10.1038/s41598-021-83008-3 (2021).
80 Alanko, V. *et al.* 27-hydroxycholesterol promotes oligodendrocyte maturation: Implications for hypercholesterolemia-associated brain white matter changes. *Glia* **71**, 1414-1428, doi:10.1002/glia.24348 (2023).
81 Anderson, A. *et al.* 7-Ketocholesterol in disease and aging. *Redox Biol* **29**, 101380, doi:10.1016/j.redox.2019.101380 (2020).
82 Mahalakshmi, K. *et al.* Influential role of 7-Ketocholesterol in the progression of Alzheimer's disease. *Prostaglandins Other Lipid Mediat* **156**, 106582, doi:10.1016/j.prostaglandins.2021.106582 (2021).
83 Cohen, S. Lipid Droplets as Organelles. *Int Rev Cell Mol Biol* **337**, 83-110, doi:10.1016/bs.ircmb.2017.12.007 (2018).
84 Valm, A. M. *et al.* Applying systems-level spectral imaging and analysis to reveal the organelle interactome. *Nature* **546**, 162-167, doi:10.1038/nature22369 (2017).
85 Shai, N. *et al.* Systematic mapping of contact sites reveals tethers and a function for the peroxisome-mitochondria contact. *Nat Commun* **9**, 1761, doi:10.1038/s41467-018-03957-8 (2018).
86 Marschallinger, J. *et al.* Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nature Neuroscience* **23**, 194-208, doi:10.1038/s41593-019-0566-1 (2020).
87 Haney, M. S. *et al.* APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. *Nature* **628**, 154-161, doi:10.1038/s41586-024-07185-7 (2024).
88 Fanning, S., Selkoe, D. & Dettmer, U. Parkinson's disease: proteinopathy or lipidopathy? *npj Parkinson's Disease* **6**, 3, doi:10.1038/s41531-019-0103-7 (2020).
89 Cantuti-Castelvetri, L. *et al.* Defective cholesterol clearance limits remyelination in the aged central nervous system. *Science* **359**, 684-688, doi:10.1126/science.aan4183 (2018).
90 Liu, L. *et al.* Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration. *Cell* **160**, 177-190, doi:10.1016/j.cell.2014.12.019 (2015).
91 Zhu, Y. *et al.* In vitro exploration of ACAT contributions to lipid droplet formation during adipogenesis. *J Lipid Res* **59**, 820-829, doi:10.1194/jlr.M081745 (2018).
92 Sienski, G. *et al.* APOE4 disrupts intracellular lipid homeostasis in human iPSC-derived glia. *Sci Transl Med* **13**, doi:10.1126/scitranslmed.aaz4564 (2021).
93 Victor, M. B. *et al.* Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. *Cell Stem Cell* **29**, 1197-1212.e1198, doi:10.1016/j.stem.2022.07.005 (2022).
94 Jarc, E. & Petan, T. A twist of FATe: Lipid droplets and inflammatory lipid mediators. *Biochimie* **169**, 69-87, doi:10.1016/j.biochi.2019.11.016 (2020).
95 Loix, M. *et al.* Perilipin-2 limits remyelination by preventing lipid droplet degradation. *Cell Mol Life Sci* **79**, 515, doi:10.1007/s00018-022-04547-0 (2022).
96 Wang, H. *et al.* Unique regulation of adipose triglyceride lipase (ATGL) by perilipin 5, a lipid droplet-associated protein. *J Biol Chem* **286**, 15707-15715, doi:10.1074/jbc.M110.207779 (2011).
97 Khatchadourian, A., Bourque, S. D., Richard, V. R., Titorenko, V. I. & Maysinger, D. Dynamics and regulation of lipid droplet formation in lipopolysaccharide (LPS)-stimulated microglia. *Biochim Biophys Acta* **1821**, 607-617, doi:10.1016/j.bbalip.2012.01.007 (2012).
98 Robb, J. L. *et al.* Blockage of ATGL-mediated breakdown of lipid droplets in microglia alleviates neuroinflammatory and behavioural responses to lipopolysaccharides. *Brain Behav Immun* **123**, 315-333, doi:10.1016/j.bbi.2024.09.027 (2025).

99 Vanherle, S. *et al.* The ApoA-I mimetic peptide 5A enhances remyelination by promoting clearance and degradation of myelin debris. *Cell Rep* **41**, 111591, doi:10.1016/j.celrep.2022.111591 (2022).
100 Hofer, P. *et al.* Cooperative lipolytic control of neuronal triacylglycerol by spastic paraplegia-associated enzyme DDHD2 and ATGL. *J Lipid Res* **64**, 100457, doi:10.1016/j.jlr.2023.100457 (2023).
101 Schonfeld, P. & Reiser, G. Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain. *J Cereb Blood Flow Metab* **33**, 1493-1499, doi:10.1038/jcbfm.2013.128 (2013).
102 Singh, R. *et al.* Autophagy regulates lipid metabolism. *Nature* **458**, 1131-1135, doi:10.1038/nature07976 (2009).
103 Griffey, C. J. & Yamamoto, A. Macroautophagy in CNS health and disease. *Nat Rev Neurosci* **23**, 411-427, doi:10.1038/s41583-022-00588-3 (2022).
104 Haidar, M., Loix, M., Bogie, J. F. J. & Hendriks, J. J. A. Lipophagy: a new player in CNS disorders. *Trends Endocrinol Metab* **32**, 941-951, doi:10.1016/j.tem.2021.08.010 (2021).
105 Nixon, R. A. & Rubinsztein, D. C. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. *Nat Rev Mol Cell Biol*, doi:10.1038/s41580-024-00757-5 (2024).
106 Haidar, M. *et al.* Targeting lipophagy in macrophages improves repair in multiple sclerosis. *Autophagy* **18**, 2697-2710, doi:10.1080/15548627.2022.2047343 (2022).
107 Tabrizi, S. J., Flower, M. D., Ross, C. A. & Wild, E. J. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. *Nat Rev Neurol* **16**, 529-546, doi:10.1038/s41582-020-0389-4 (2020).
108 Rui, Y. N. *et al.* Huntingtin functions as a scaffold for selective macroautophagy. *Nat Cell Biol* **17**, 262-275, doi:10.1038/ncb3101 (2015).
109 Kloska, A., Wesierska, M., Malinowska, M., Gabig-Ciminska, M. & Jakobkiewicz-Banecka, J. Lipophagy and Lipolysis Status in Lipid Storage and Lipid Metabolism Diseases. *Int J Mol Sci* **21**, doi:10.3390/ijms21176113 (2020).
110 Wong, D. A., Bassilian, S., Lim, S. & Paul Lee, W. N. Coordination of peroxisomal beta-oxidation and fatty acid elongation in HepG2 cells. *J Biol Chem* **279**, 41302-41309, doi:10.1074/jbc.M406766200 (2004).
111 Cui, W. *et al.* Lipophagy-derived fatty acids undergo extracellular efflux via lysosomal exocytosis. *Autophagy* **17**, 690-705, doi:10.1080/15548627.2020.1728097 (2021).
112 Ouimet, M. *et al.* Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. *Cell Metab* **13**, 655-667, doi:10.1016/j.cmet.2011.03.023 (2011).
113 Haemmerle, G. *et al.* ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-alpha and PGC-1. *Nat Med* **17**, 1076-1085, doi:10.1038/nm.2439 (2011).
114 Mathiowetz, A. J. & Olzmann, J. A. Lipid droplets and cellular lipid flux. *Nat Cell Biol* **26**, 331-345, doi:10.1038/s41556-024-01364-4 (2024).
115 Tavasoli, M., Lahire, S., Reid, T., Brodovsky, M. & McMaster, C. R. Genetic diseases of the Kennedy pathways for membrane synthesis. *J Biol Chem* **295**, 17877-17886, doi:10.1074/jbc.REV120.013529 (2020).
116 Gibellini, F. & Smith, T. K. The Kennedy pathway--De novo synthesis of phosphatidylethanolamine and phosphatidylcholine. *IUBMB Life* **62**, 414-428, doi:10.1002/iub.337 (2010).
117 Eichmann, T. O. & Lass, A. DAG tales: the multiple faces of diacylglycerol--stereochemistry, metabolism, and signaling. *Cell Mol Life Sci* **72**, 3931-3952, doi:10.1007/s00018-015-1982-3 (2015).
118 Skripuletz, T. *et al.* Pivotal role of choline metabolites in remyelination. *Brain* **138**, 398-413, doi:10.1093/brain/awu358 (2015).
119 Magaquian, D., Delgado Ocana, S., Perez, C. & Banchio, C. Phosphatidylcholine restores neuronal plasticity of neural stem cells under inflammatory stress. *Sci Rep* **11**, 22891, doi:10.1038/s41598-021-02361-5 (2021).

120 Guttenplan, K. A. *et al.* Neurotoxic reactive astrocytes induce cell death via saturated lipids. *Nature* **599**, 102-107, doi:10.1038/s41586-021-03960-y (2021).
121 Mi, Y. *et al.* Loss of fatty acid degradation by astrocytic mitochondria triggers neuroinflammation and neurodegeneration. *Nat Metab* **5**, 445-465, doi:10.1038/s42255-023-00756-4 (2023).
122 Fitz, N. F. *et al.* Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. *Nat Commun* **12**, 3416, doi:10.1038/s41467-021-23762-0 (2021).
123 Hachem, M., Ahmmed, M. K. & Nacir-Delord, H. Phospholipidomics in Clinical Trials for Brain Disorders: Advancing our Understanding and Therapeutic Potentials. *Mol Neurobiol* **61**, 3272-3295, doi:10.1007/s12035-023-03793-y (2024).
124 Schutter, M., Giavalisco, P., Brodesser, S. & Graef, M. Local Fatty Acid Channeling into Phospholipid Synthesis Drives Phagophore Expansion during Autophagy. *Cell* **180**, 135-149 e114, doi:10.1016/j.cell.2019.12.005 (2020).
125 Kim, J. W., Lee, J. Y., Oh, M. & Lee, E. W. An integrated view of lipid metabolism in ferroptosis revisited via lipidomic analysis. *Exp Mol Med* **55**, 1620-1631, doi:10.1038/s12276-023-01077-y (2023).
126 Bazinet, R. P., Rao, J. S., Chang, L., Rapoport, S. I. & Lee, H. J. Chronic carbamazepine decreases the incorporation rate and turnover of arachidonic acid but not docosahexaenoic acid in brain phospholipids of the unanesthetized rat: relevance to bipolar disorder. *Biol Psychiatry* **59**, 401-407, doi:10.1016/j.biopsych.2005.07.024 (2006).
127 Bazinet, R. P., Rao, J. S., Chang, L., Rapoport, S. I. & Lee, H. J. Chronic valproate does not alter the kinetics of docosahexaenoic acid within brain phospholipids of the unanesthetized rat. *Psychopharmacology (Berl)* **182**, 180-185, doi:10.1007/s00213-005-0059-7 (2005).
128 Lee, H. J. *et al.* Topiramate does not alter the kinetics of arachidonic or docosahexaenoic acid in brain phospholipids of the unanesthetized rat. *Neurochem Res* **30**, 677-683, doi:10.1007/s11064-005-2756-3 (2005).
129 Cunningham, T. J. *et al.* Secreted phospholipase A2 activity in experimental autoimmune encephalomyelitis and multiple sclerosis. *J Neuroinflammation* **3**, 26, doi:10.1186/1742-2094-3-26 (2006).
130 Lee, G., Kang, G.-H. & Bae, H. Bee venom phospholipase A2 suppression of experimental autoimmune encephalomyelitis is dependent on its enzymatic activity. *Molecular & Cellular Toxicology* **15**, 307-313, doi:10.1007/s13273-019-0034-8 (2019).
131 Chung, E. S. *et al.* Neuro-protective effects of bee venom by suppression of neuroinflammatory responses in a mouse model of Parkinson's disease: role of regulatory T cells. *Brain Behav Immun* **26**, 1322-1330, doi:10.1016/j.bbi.2012.08.013 (2012).
132 Kim, K. H. *et al.* Dose-Dependent Neuroprotective Effect of Standardized Bee Venom Phospholipase A(2) Against MPTP-Induced Parkinson's Disease in Mice. *Front Aging Neurosci* **11**, 80, doi:10.3389/fnagi.2019.00080 (2019).
133 Sagy-Bross, C. *et al.* The role of cytosolic phospholipase A2 alpha in amyloid precursor protein induction by amyloid beta1-42 : implication for neurodegeneration. *J Neurochem* **132**, 559-571, doi:10.1111/jnc.13012 (2015).
134 Sanchez-Mejia, R. O. *et al.* Phospholipase A2 reduction ameliorates cognitive deficits in a mouse model of Alzheimer's disease. *Nat Neurosci* **11**, 1311-1318, doi:10.1038/nn.2213 (2008).
135 Ham, H. J. *et al.* Bee venom phospholipase A2 ameliorates amyloidogenesis and neuroinflammation through inhibition of signal transducer and activator of transcription-3 pathway in Tg2576 mice. *Transl Neurodegener* **8**, 26, doi:10.1186/s40035-019-0167-7 (2019).
136 Sumi-Akamaru, H. *et al.* High expression of alpha-synuclein in damaged mitochondria with PLA2G6 dysfunction. *Acta Neuropathol Commun* **4**, 27, doi:10.1186/s40478-016-0298-3 (2016).

137 Lin, G. *et al.* Phospholipase PLA2G6, a Parkinsonism-Associated Gene, Affects Vps26 and Vps35, Retromer Function, and Ceramide Levels, Similar to alpha-Synuclein Gain. *Cell Metab* **28**, 605-618 e606, doi:10.1016/j.cmet.2018.05.019 (2018).
138 Mori, A. *et al.* Parkinson's disease-associated iPLA2-VIA/PLA2G6 regulates neuronal functions and alpha-synuclein stability through membrane remodeling. *Proc Natl Acad Sci U S A* **116**, 20689-20699, doi:10.1073/pnas.1902958116 (2019).
139 Morgan, N. V. *et al.* PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat Genet* **38**, 752-754, doi:10.1038/ng1826 (2006).
140 Lu, C. S. *et al.* PLA2G6 mutations in PARK14-linked young-onset parkinsonism and sporadic Parkinson's disease. *Am J Med Genet B Neuropsychiatr Genet* **159B**, 183-191, doi:10.1002/ajmg.b.32012 (2012).
141 Kalyvas, A. *et al.* Differing roles for members of the phospholipase A2 superfamily in experimental autoimmune encephalomyelitis. *Brain* **132**, 1221-1235, doi:10.1093/brain/awp002 (2009).
142 Khan, S. A. & Ilies, M. A. The Phospholipase A2 Superfamily: Structure, Isozymes, Catalysis, Physiologic and Pathologic Roles. *Int J Mol Sci* **24**, doi:10.3390/ijms24021353 (2023).
143 Nicholatos, J. W., Tran, D., Liu, Y., Hirst, W. D. & Weihofen, A. Lysophosphatidylcholine acyltransferase 1 promotes pathology and toxicity in two distinct cell-based alpha-synuclein models. *Neurosci Lett* **772**, 136491, doi:10.1016/j.neulet.2022.136491 (2022).
144 Eto, M., Shindou, H., Yamamoto, S., Tamura-Nakano, M. & Shimizu, T. Lysophosphatidylethanolamine acyltransferase 2 (LPEAT2) incorporates DHA into phospholipids and has possible functions for fatty acid-induced cell death. *Biochem Biophys Res Commun* **526**, 246-252, doi:10.1016/j.bbrc.2020.03.074 (2020).
145 Bargui, R. *et al.* Phospholipids: Identification and Implication in Muscle Pathophysiology. *Int J Mol Sci* **22**, doi:10.3390/ijms22158176 (2021).
146 Yin, J. *et al.* Brain-specific lipoprotein receptors interact with astrocyte derived apolipoprotein and mediate neuron-glia lipid shuttling. *Nat Commun* **12**, 2408, doi:10.1038/s41467-021-22751-7 (2021).
147 Mauch, D. H. *et al.* CNS synaptogenesis promoted by glia-derived cholesterol. *Science* **294**, 1354-1357, doi:10.1126/science.294.5545.1354 (2001).
148 Barnes-Velez, J. A., Aksoy Yasar, F. B. & Hu, J. Myelin lipid metabolism and its role in myelination and myelin maintenance. *Innovation (Camb)* **4**, 100360, doi:10.1016/j.xinn.2022.100360 (2023).
149 Jackson, R. J., Hyman, B. T. & Serrano-Pozo, A. Multifaceted roles of APOE in Alzheimer disease. *Nat Rev Neurol* **20**, 457-474, doi:10.1038/s41582-024-00988-2 (2024).
150 Hayashi, H., Campenot, R. B., Vance, D. E. & Vance, J. E. Glial lipoproteins stimulate axon growth of central nervous system neurons in compartmented cultures. *J Biol Chem* **279**, 14009-14015, doi:10.1074/jbc.M313828200 (2004).
151 Szrok-Jurga, S. *et al.* The Role of Acyl-CoA beta-Oxidation in Brain Metabolism and Neurodegenerative Diseases. *Int J Mol Sci* **24**, doi:10.3390/ijms241813977 (2023).
152 Chen, Y., Strickland, M. R., Soranno, A. & Holtzman, D. M. Apolipoprotein E: Structural Insights and Links to Alzheimer Disease Pathogenesis. *Neuron* **109**, 205-221, doi:10.1016/j.neuron.2020.10.008 (2021).
153 Mahley, R. W. Central Nervous System Lipoproteins: ApoE and Regulation of Cholesterol Metabolism. *Arterioscler Thromb Vasc Biol* **36**, 1305-1315, doi:10.1161/atvbaha.116.307023 (2016).
154 van Deijk, A. F. *et al.* Astrocyte lipid metabolism is critical for synapse development and function in vivo. *Glia* **65**, 670-682, doi:10.1002/glia.23120 (2017).
155 Ferris, H. A. *et al.* Loss of astrocyte cholesterol synthesis disrupts neuronal function and alters whole-body metabolism. *Proc Natl Acad Sci U S A* **114**, 1189-1194, doi:10.1073/pnas.1620506114 (2017).

156 Valenza, M. *et al.* Disruption of astrocyte-neuron cholesterol cross talk affects neuronal function in Huntington's disease. *Cell Death Differ* **22**, 690-702, doi:10.1038/cdd.2014.162 (2015).
157 Liu, L., MacKenzie, K. R., Putluri, N., Maletic-Savatic, M. & Bellen, H. J. The Glia-Neuron Lactate Shuttle and Elevated ROS Promote Lipid Synthesis in Neurons and Lipid Droplet Accumulation in Glia via APOE/D. *Cell Metab* **26**, 719-737 e716, doi:10.1016/j.cmet.2017.08.024 (2017).
158 Qi, G. *et al.* ApoE4 Impairs Neuron-Astrocyte Coupling of Fatty Acid Metabolism. *Cell Rep* **34**, 108572, doi:10.1016/j.celrep.2020.108572 (2021).
159 Ioannou, M. S. *et al.* Neuron-Astrocyte Metabolic Coupling Protects against Activity-Induced Fatty Acid Toxicity. *Cell* **177**, 1522-1535 e1514, doi:10.1016/j.cell.2019.04.001 (2019).
160 Targa Dias Anastacio, H., Matosin, N. & Ooi, L. Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype? *Transl Psychiatry* **12**, 257, doi:10.1038/s41398-022-02024-7 (2022).
161 Haba, K., Ogawa, N., Mizukawa, K. & Mori, A. Time course of changes in lipid peroxidation, pre- and postsynaptic cholinergic indices, NMDA receptor binding and neuronal death in the gerbil hippocampus following transient ischemia. *Brain Res* **540**, 116-122, doi:10.1016/0006-8993(91)90497-j (1991).
162 Parihar, M. S. & Hemnani, T. Experimental excitotoxicity provokes oxidative damage in mice brain and attenuation by extract of Asparagus racemosus. *J Neural Transm (Vienna)* **111**, 1-12, doi:10.1007/s00702-003-0069-8 (2004).
163 Haynes, P. R. *et al.* A neuron-glia lipid metabolic cycle couples daily sleep to mitochondrial homeostasis. *Nat Neurosci* **27**, 666-678, doi:10.1038/s41593-023-01568-1 (2024).
164 Nitz, D. A., van Swinderen, B., Tononi, G. & Greenspan, R. J. Electrophysiological correlates of rest and activity in Drosophila melanogaster. *Curr Biol* **12**, 1934-1940, doi:10.1016/s0960-9822(02)01300-3 (2002).
165 Liddelow, S. A. *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481-487, doi:10.1038/nature21029 (2017).
166 Guttenplan, K. A. *et al.* Neurotoxic Reactive Astrocytes Drive Neuronal Death after Retinal Injury. *Cell Rep* **31**, 107776, doi:10.1016/j.celrep.2020.107776 (2020).
167 Lindner, K. *et al.* Isoform- and cell-state-specific lipidation of ApoE in astrocytes. *Cell Rep* **38**, 110435, doi:10.1016/j.celrep.2022.110435 (2022).
168 Franklin, R. J. & Ffrench-Constant, C. Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci* **9**, 839-855, doi:10.1038/nrn2480 (2008).
169 Voskuhl, R. R. *et al.* Gene expression in oligodendrocytes during remyelination reveals cholesterol homeostasis as a therapeutic target in multiple sclerosis. *Proc Natl Acad Sci U S A* **116**, 10130-10139, doi:10.1073/pnas.1821306116 (2019).
170 Khandker, L. *et al.* Cholesterol biosynthesis defines oligodendrocyte precursor heterogeneity between brain and spinal cord. *Cell Rep* **38**, 110423, doi:10.1016/j.celrep.2022.110423 (2022).
171 Berghoff, S. A. *et al.* Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. *Nat Neurosci* **24**, 47-60, doi:10.1038/s41593-020-00757-6 (2021).
172 O'Brien, J. S. STABILITY OF THE MYELIN MEMBRANE. *Science* **147**, 1099-1107, doi:10.1126/science.147.3662.1099 (1965).
173 Grajchen, E., Hendriks, J. J. A. & Bogie, J. F. J. The physiology of foamy phagocytes in multiple sclerosis. *Acta Neuropathol Commun* **6**, 124, doi:10.1186/s40478-018-0628-8 (2018).
174 Mailleux, J. *et al.* Active liver X receptor signaling in phagocytes in multiple sclerosis lesions. *Mult Scler* **24**, 279-289, doi:10.1177/1352458517696595 (2018).
175 Bogie, J. F. *et al.* Myelin-derived lipids modulate macrophage activity by liver X receptor activation. *PLoS One* **7**, e44998, doi:10.1371/journal.pone.0044998 (2012).

176 Spann, N. J. *et al.* Regulated accumulation of desmosterol integrates macrophage lipid metabolism and inflammatory responses. *Cell* **151**, 138-152, doi:10.1016/j.cell.2012.06.054 (2012).
177 Zhang, R. *et al.* Enhanced liver X receptor signalling reduces brain injury and promotes tissue regeneration following experimental intracerebral haemorrhage: roles of microglia/macrophages. *Stroke Vasc Neurol* **8**, 486-502, doi:10.1136/svn-2023-002331 (2023).
178 Ruckh, J. M. *et al.* Rejuvenation of regeneration in the aging central nervous system. *Cell Stem Cell* **10**, 96-103, doi:10.1016/j.stem.2011.11.019 (2012).
179 Natrajan, M. S. *et al.* Retinoid X receptor activation reverses age-related deficiencies in myelin debris phagocytosis and remyelination. *Brain* **138**, 3581-3597, doi:10.1093/brain/awv289 (2015).
180 Franklin, R. J. M., Frisen, J. & Lyons, D. A. Revisiting remyelination: Towards a consensus on the regeneration of CNS myelin. *Semin Cell Dev Biol* **116**, 3-9, doi:10.1016/j.semcdb.2020.09.009 (2021).
181 Lampron, A. *et al.* Inefficient clearance of myelin debris by microglia impairs remyelinating processes. *J Exp Med* **212**, 481-495, doi:10.1084/jem.20141656 (2015).
182 Berghoff, S. A. *et al.* Dietary cholesterol promotes repair of demyelinated lesions in the adult brain. *Nat Commun* **8**, 14241, doi:10.1038/ncomms14241 (2017).
183 Camargo, N. *et al.* Oligodendroglial myelination requires astrocyte-derived lipids. *PLoS Biol* **15**, e1002605, doi:10.1371/journal.pbio.1002605 (2017).
184 Molina-Gonzalez, I. *et al.* Astrocyte-oligodendrocyte interaction regulates central nervous system regeneration. *Nat Commun* **14**, 3372, doi:10.1038/s41467-023-39046-8 (2023).
185 Tanaka, Y. *et al.* NF-E2-related factor 2 inhibits lipid accumulation and oxidative stress in mice fed a high-fat diet. *J Pharmacol Exp Ther* **325**, 655-664, doi:10.1124/jpet.107.135822 (2008).
186 Levings, D. C., Pathak, S. S., Yang, Y. M. & Slattery, M. Limited expression of Nrf2 in neurons across the central nervous system. *Redox Biol* **65**, 102830, doi:10.1016/j.redox.2023.102830 (2023).
187 Vanherle, S., Haidar, M., Irobi, J., Bogie, J. F. J. & Hendriks, J. J. A. Extracellular vesicle-associated lipids in central nervous system disorders. *Adv Drug Deliv Rev* **159**, 322-331, doi:10.1016/j.addr.2020.04.011 (2020).
188 Lombardi, M. *et al.* Detrimental and protective action of microglial extracellular vesicles on myelin lesions: astrocyte involvement in remyelination failure. *Acta Neuropathol* **138**, 987-1012, doi:10.1007/s00401-019-02049-1 (2019).
189 Lombardi, M. *et al.* Extracellular vesicles released by microglia and macrophages carry endocannabinoids which foster oligodendrocyte differentiation. *Front Immunol* **15**, 1331210, doi:10.3389/fimmu.2024.1331210 (2024).
190 Yuana, Y., Levels, J., Grootemaat, A., Sturk, A. & Nieuwland, R. Co-isolation of extracellular vesicles and high-density lipoproteins using density gradient ultracentrifugation. *J Extracell Vesicles* **3**, doi:10.3402/jev.v3.23262 (2014).
191 Wang, G. *et al.* Astrocytes secrete exosomes enriched with proapoptotic ceramide and prostate apoptosis response 4 (PAR-4): potential mechanism of apoptosis induction in Alzheimer disease (AD). *J Biol Chem* **287**, 21384-21395, doi:10.1074/jbc.M112.340513 (2012).
192 Yuyama, K. *et al.* A potential function for neuronal exosomes: sequestering intracerebral amyloid-β peptide. *FEBS Lett* **589**, 84-88, doi:10.1016/j.febslet.2014.11.027 (2015).
193 Yuyama, K. *et al.* Decreased amyloid-β pathologies by intracerebral loading of glycosphingolipid-enriched exosomes in Alzheimer model mice. *J Biol Chem* **289**, 24488-24498, doi:10.1074/jbc.M114.577213 (2014).
194 Yuyama, K., Sun, H., Mitsutake, S. & Igarashi, Y. Sphingolipid-modulated exosome secretion promotes clearance of amyloid-β by microglia. *J Biol Chem* **287**, 10977-10989, doi:10.1074/jbc.M111.324616 (2012).

195 Yuyama, K., Mitsutake, S. & Igarashi, Y. Pathological roles of ceramide and its metabolites in metabolic syndrome and Alzheimer's disease. *Biochim Biophys Acta* **1841**, 793-798, doi:10.1016/j.bbalip.2013.08.002 (2014).
196 Kurzawa-Akanbi, M. *et al.* Altered ceramide metabolism is a feature in the extracellular vesicle-mediated spread of alpha-synuclein in Lewy body disorders. *Acta Neuropathol* **142**, 961-984, doi:10.1007/s00401-021-02367-3 (2021).
197 Grey, M. *et al.* Acceleration of α-synuclein aggregation by exosomes. *J Biol Chem* **290**, 2969-2982, doi:10.1074/jbc.M114.585703 (2015).
198 Kopatz, V. *et al.* Micro- and Nanoplastics Breach the Blood-Brain Barrier (BBB): Biomolecular Corona's Role Revealed. *Nanomaterials (Basel)* **13**, doi:10.3390/nano13081404 (2023).
199 Hu, M. & Palic, D. Micro- and nano-plastics activation of oxidative and inflammatory adverse outcome pathways. *Redox Biol* **37**, 101620, doi:10.1016/j.redox.2020.101620 (2020).
200 Prust, M., Meijer, J. & Westerink, R. H. S. The plastic brain: neurotoxicity of micro- and nanoplastics. *Part Fibre Toxicol* **17**, 24, doi:10.1186/s12989-020-00358-y (2020).
201 Min, H., Yang, Y. Y. & Yang, Y. Cold induces brain region-selective neuronal activity-dependent lipid metabolism. *bioRxiv*, doi:10.1101/2024.04.15.589506 (2024).
202 Leiria, L. O. *et al.* 12-Lipoxygenase Regulates Cold Adaptation and Glucose Metabolism by Producing the Omega-3 Lipid 12-HEPE from Brown Fat. *Cell Metab* **30**, 768-783 e767, doi:10.1016/j.cmet.2019.07.001 (2019).
203 Marcher, A. B. *et al.* RNA-Seq and Mass-Spectrometry-Based Lipidomics Reveal Extensive Changes of Glycerolipid Pathways in Brown Adipose Tissue in Response to Cold. *Cell Rep* **13**, 2000-2013, doi:10.1016/j.celrep.2015.10.069 (2015).
204 Chen, W. *et al.* Cold exposure alters lipid metabolism of skeletal muscle through HIF-1alpha-induced mitophagy. *BMC Biol* **21**, 27, doi:10.1186/s12915-023-01514-4 (2023).
205 Huang, D. *et al.* Cold exposure impairs extracellular vesicle swarm-mediated nasal antiviral immunity. *J Allergy Clin Immunol* **151**, 509-525 e508, doi:10.1016/j.jaci.2022.09.037 (2023).
206 Briaud, P. *et al.* Temperature Influences the Composition and Cytotoxicity of Extracellular Vesicles in Staphylococcus aureus. *mSphere* **6**, e0067621, doi:10.1128/mSphere.00676-21 (2021).
207 Jaroslawska, J., Gospodarska, E. & Korytko, A. Increasing energy expenditure through exercise and low ambient temperature offers oxidative protection to the hypothalamus after high-fat feeding to mice. *J Neuroendocrinol* **34**, e13095, doi:10.1111/jne.13095 (2022).
208 Dias, S. S. G. *et al.* Metabolic reprogramming and lipid droplets are involved in Zika virus replication in neural cells. *J Neuroinflammation* **20**, 61, doi:10.1186/s12974-023-02736-7 (2023).
209 Monson, E. A. *et al.* Intracellular lipid droplet accumulation occurs early following viral infection and is required for an efficient interferon response. *Nat Commun* **12**, 4303, doi:10.1038/s41467-021-24632-5 (2021).
210 Matveeva, O. *et al.* Western lifestyle and immunopathology of multiple sclerosis. *Ann N Y Acad Sci* **1417**, 71-86, doi:10.1111/nyas.13583 (2018).
211 Custers, Emma, E. M., Kiliaan & Amanda, J. Dietary lipids from body to brain. *Prog Lipid Res* **85**, 101144, doi:10.1016/j.plipres.2021.101144 (2022).
212 Bosch-Queralt, M. *et al.* Diet-dependent regulation of TGFbeta impairs reparative innate immune responses after demyelination. *Nat Metab* **3**, 211-227, doi:10.1038/s42255-021-00341-7 (2021).
213 Liemisa, B. *et al.* Brain apolipoprotein E levels in mice challenged by a Western diet increase in an allele-dependent manner. *Aging Brain* **4**, 100102, doi:10.1016/j.nbas.2023.100102 (2023).
214 Li, Q. *et al.* Impaired lipophagy induced-microglial lipid droplets accumulation contributes to the buildup of TREM1 in diabetes-associated cognitive impairment. *Autophagy* **19**, 2639-2656, doi:10.1080/15548627.2023.2213984 (2023).

215 Morselli, E., Criollo, A., Rodriguez-Navas, C. & Clegg, D. J. Chronic High Fat Diet Consumption Impairs Metabolic Health of Male Mice. *Inflamm Cell Signal* **1**, e561, doi:10.14800/ics.561 (2014).
216 Tan, B. L. & Norhaizan, M. E. Effect of High-Fat Diets on Oxidative Stress, Cellular Inflammatory Response and Cognitive Function. *Nutrients* **11**, doi:10.3390/nu11112579 (2019).
217 Lee, J. C. *et al.* High-fat diet-induced lipidome perturbations in the cortex, hippocampus, hypothalamus, and olfactory bulb of mice. *Biochim Biophys Acta Mol Cell Biol Lipids* **1863**, 980-990, doi:10.1016/j.bbalip.2018.05.007 (2018).
218 Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M. & Cheng, A. Intermittent metabolic switching, neuroplasticity and brain health. *Nat Rev Neurosci* **19**, 63-80, doi:10.1038/nrn.2017.156 (2018).
219 Logan, R. W. & McClung, C. A. Rhythms of life: circadian disruption and brain disorders across the lifespan. *Nat Rev Neurosci* **20**, 49-65, doi:10.1038/s41583-018-0088-y (2019).
220 Lee, C. H., Murrell, C. E., Chu, A. & Pan, X. Circadian Regulation of Apolipoproteins in the Brain: Implications in Lipid Metabolism and Disease. *Int J Mol Sci* **24**, doi:10.3390/ijms242417415 (2023).
221 Sheehan, P. W. *et al.* A glial circadian gene expression atlas reveals cell type and disease-specific reprogramming in response to amyloid pathology or aging. *bioRxiv*, doi:10.1101/2024.05.28.596297 (2024).
222 Matsumoto, K. *et al.* Psychological stress-induced enhancement of brain lipid peroxidation via nitric oxide systems and its modulation by anxiolytic and anxiogenic drugs in mice. *Brain Res* **839**, 74-84, doi:10.1016/s0006-8993(99)01715-1 (1999).
223 Lee, H., Park, J. & Kim, S. Metabolic and Transcriptomic Signatures of the Acute Psychological Stress Response in the Mouse Brain. *Metabolites* **13**, doi:10.3390/metabo13030453 (2023).
224 von Ziegler, L. M. *et al.* Multiomic profiling of the acute stress response in the mouse hippocampus. *Nat Commun* **13**, 1824, doi:10.1038/s41467-022-29367-5 (2022).
225 Salvador, A. F., Shyu, C. R. & Parks, E. J. Measurement of lipid flux to advance translational research: evolution of classic methods to the future of precision health. *Exp Mol Med* **54**, 1348-1353, doi:10.1038/s12276-022-00838-5 (2022).
226 Ellis, S. R. *et al.* Mass spectrometry imaging of phosphatidylcholine metabolism in lungs administered with therapeutic surfactants and isotopic tracers. *J Lipid Res* **62**, 100023, doi:10.1016/j.jlr.2021.100023 (2021).
227 Bowman, A. P. *et al.* Evaluation of lipid coverage and high spatial resolution MALDI-imaging capabilities of oversampling combined with laser post-ionisation. *Anal Bioanal Chem* **412**, 2277-2289, doi:10.1007/s00216-019-02290-3 (2020).
228 Chen, T., Yavuz, A. & Wang, M. C. Dissecting lipid droplet biology with coherent Raman scattering microscopy. *J Cell Sci* **135**, doi:10.1242/jcs.252353 (2022).
229 Uematsu, M. & Shimizu, T. Raman microscopy-based quantification of the physical properties of intracellular lipids. *Commun Biol* **4**, 1176, doi:10.1038/s42003-021-02679-w (2021).
230 Folick, A., Min, W. & Wang, M. C. Label-free imaging of lipid dynamics using Coherent Anti-stokes Raman Scattering (CARS) and Stimulated Raman Scattering (SRS) microscopy. *Curr Opin Genet Dev* **21**, 585-590, doi:10.1016/j.gde.2011.09.003 (2011).
231 Shi, L. & Tu, B. P. Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. *Curr Opin Cell Biol* **33**, 125-131, doi:10.1016/j.ceb.2015.02.003 (2015).
232 Morita, S. Y. & Terada, T. Enzymatic measurement of phosphatidylglycerol and cardiolipin in cultured cells and mitochondria. *Sci Rep* **5**, 11737, doi:10.1038/srep11737 (2015).
233 Stone, S. J. *et al.* The endoplasmic reticulum enzyme DGAT2 is found in mitochondria-associated membranes and has a mitochondrial targeting signal that promotes its association with mitochondria. *J Biol Chem* **284**, 5352-5361, doi:10.1074/jbc.M805768200 (2009).
234 Huitema, K., van den Dikkenberg, J., Brouwers, J. F. & Holthuis, J. C. Identification of a family of animal sphingomyelin synthases. *Embo j* **23**, 33-44, doi:10.1038/sj.emboj.7600034 (2004).

235 Hanada, K., Kumagai, K., Tomishige, N. & Yamaji, T. CERT-mediated trafficking of ceramide. *Biochim Biophys Acta* **1791**, 684-691, doi:10.1016/j.bbalip.2009.01.006 (2009).
236 Honsho, M., Tanaka, M., Zoeller, R. A. & Fujiki, Y. Distinct Functions of Acyl/Alkyl Dihydroxyacetonephosphate Reductase in Peroxisomes and Endoplasmic Reticulum. *Front Cell Dev Biol* **8**, 855, doi:10.3389/fcell.2020.00855 (2020).
237 Schlame, M. & Haldar, D. Cardiolipin is synthesized on the matrix side of the inner membrane in rat liver mitochondria. *J Biol Chem* **268**, 74-79 (1993).
238 Rusiñol, A. E., Cui, Z., Chen, M. H. & Vance, J. E. A unique mitochondria-associated membrane fraction from rat liver has a high capacity for lipid synthesis and contains pre-Golgi secretory proteins including nascent lipoproteins. *J Biol Chem* **269**, 27494-27502 (1994).
239 Kinney, A. J. & Carman, G. M. Enzymes of phosphoinositide synthesis in secretory vesicles destined for the plasma membrane in Saccharomyces cerevisiae. *J Bacteriol* **172**, 4115-4117, doi:10.1128/jb.172.7.4115-4117.1990 (1990).
240 Gaigg, B., Simbeni, R., Hrastnik, C., Paltauf, F. & Daum, G. Characterization of a microsomal subfraction associated with mitochondria of the yeast, Saccharomyces cerevisiae. Involvement in synthesis and import of phospholipids into mitochondria. *Biochim Biophys Acta* **1234**, 214-220, doi:10.1016/0005-2736(94)00287-y (1995).
241 O'Donnell, V. B. New appreciation for an old pathway: the Lands Cycle moves into new arenas in health and disease. *Biochem Soc Trans* **50**, 1-11, doi:10.1042/BST20210579 (2022).
242 Ferrara, P. J. *et al.* Lysophospholipid acylation modulates plasma membrane lipid organization and insulin sensitivity in skeletal muscle. *J Clin Invest* **131**, doi:10.1172/JCI135963 (2021).
243 Kamp, F. & Hamilton, J. A. pH gradients across phospholipid membranes caused by fast flip-flop of un-ionized fatty acids. *Proc Natl Acad Sci U S A* **89**, 11367-11370, doi:10.1073/pnas.89.23.11367 (1992).
244 Chen, C. T., Ma, D. W., Kim, J. H., Mount, H. T. & Bazinet, R. P. The low density lipoprotein receptor is not necessary for maintaining mouse brain polyunsaturated fatty acid concentrations. *J Lipid Res* **49**, 147-152, doi:10.1194/jlr.M700386-JLR200 (2008).
245 Mitchell, R. W., On, N. H., Del Bigio, M. R., Miller, D. W. & Hatch, G. M. Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells. *J Neurochem* **117**, 735-746, doi:10.1111/j.1471-4159.2011.07245.x (2011).
246 Mitchell, R. W., Edmundson, C. L., Miller, D. W. & Hatch, G. M. On the mechanism of oleate transport across human brain microvessel endothelial cells. *J Neurochem* **110**, 1049-1057, doi:10.1111/j.1471-4159.2009.06199.x (2009).
247 Pan, Y. *et al.* Fatty Acid-Binding Protein 5 Facilitates the Blood-Brain Barrier Transport of Docosahexaenoic Acid. *Mol Pharm* **12**, 4375-4385, doi:10.1021/acs.molpharmaceut.5b00580 (2015).
248 Ochiai, Y. *et al.* The blood-brain barrier fatty acid transport protein 1 (FATP1/SLC27A1) supplies docosahexaenoic acid to the brain, and insulin facilitates transport. *J Neurochem* **141**, 400-412, doi:10.1111/jnc.13943 (2017).
249 Pan, Y. *et al.* Fatty Acid-Binding Protein 5 at the Blood-Brain Barrier Regulates Endogenous Brain Docosahexaenoic Acid Levels and Cognitive Function. *J Neurosci* **36**, 11755-11767, doi:10.1523/JNEUROSCI.1583-16.2016 (2016).
250 Nguyen, L. N. *et al.* Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature* **509**, 503-506, doi:10.1038/nature13241 (2014).
251 Cater, R. J. *et al.* Structural basis of omega-3 fatty acid transport across the blood-brain barrier. *Nature* **595**, 315-319, doi:10.1038/s41586-021-03650-9 (2021).
252 Fernandez, R. F. *et al.* Acyl-CoA synthetase 6 enriches the neuroprotective omega-3 fatty acid DHA in the brain. *Proc Natl Acad Sci U S A* **115**, 12525-12530, doi:10.1073/pnas.1807958115 (2018).

253 Oldendorf, W. H. Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. *Am J Physiol* **224**, 1450-1453, doi:10.1152/ajplegacy.1973.224.6.1450 (1973).
254 Sun, J. *et al.* Clostridium butyricum pretreatment attenuates cerebral ischemia/reperfusion injury in mice via anti-oxidation and anti-apoptosis. *Neurosci Lett* **613**, 30-35, doi:10.1016/j.neulet.2015.12.047 (2016).
255 Vijay, N. & Morris, M. E. Role of monocarboxylate transporters in drug delivery to the brain. *Curr Pharm Des* **20**, 1487-1498, doi:10.2174/13816128113199990462 (2014).
256 Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol* **16**, 461-478, doi:10.1038/s41575-019-0157-3 (2019).
257 Chen, J., Zhang, X., Kusumo, H., Costa, L. G. & Guizzetti, M. Cholesterol efflux is differentially regulated in neurons and astrocytes: implications for brain cholesterol homeostasis. *Biochim Biophys Acta* **1831**, 263-275, doi:10.1016/j.bbalip.2012.09.007 (2013).
258 Kim, W. S., Weickert, C. S. & Garner, B. Role of ATP-binding cassette transporters in brain lipid transport and neurological disease. *J Neurochem* **104**, 1145-1166, doi:10.1111/j.1471-4159.2007.05099.x (2008).
259 Flowers, S. A. & Rebeck, G. W. APOE in the normal brain. *Neurobiol Dis* **136**, 104724, doi:10.1016/j.nbd.2019.104724 (2020).
260 Chen, J., Li, Q. & Wang, J. Topology of human apolipoprotein E3 uniquely regulates its diverse biological functions. *Proc Natl Acad Sci U S A* **108**, 14813-14818, doi:10.1073/pnas.1106420108 (2011).
261 Feringa, F. M. & van der Kant, R. Cholesterol and Alzheimer's Disease; From Risk Genes to Pathological Effects. *Front Aging Neurosci* **13**, 690372, doi:10.3389/fnagi.2021.690372 (2021).
262 Raulin, A. C., Martens, Y. A. & Bu, G. Lipoproteins in the Central Nervous System: From Biology to Pathobiology. *Annu Rev Biochem* **91**, 731-759, doi:10.1146/annurev-biochem-032620-104801 (2022).
263 Bohlen, C. J. *et al.* Diverse Requirements for Microglial Survival, Specification, and Function Revealed by Defined-Medium Cultures. *Neuron* **94**, 759-773 e758, doi:10.1016/j.neuron.2017.04.043 (2017).
264 Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C. & Sheng, M. TREM2 Binds to Apolipoproteins, Including APOE and CLU/APOJ, and Thereby Facilitates Uptake of Amyloid-Beta by Microglia. *Neuron* **91**, 328-340, doi:10.1016/j.neuron.2016.06.015 (2016).
265 Saher, G. & Stumpf, S. K. Cholesterol in myelin biogenesis and hypomyelinating disorders. *Biochim Biophys Acta* **1851**, 1083-1094, doi:10.1016/j.bbalip.2015.02.010 (2015).
266 Liu, C. C., Liu, C. C., Kanekiyo, T., Xu, H. & Bu, G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* **9**, 106-118, doi:10.1038/nrneurol.2012.263 (2013).
267 Tcw, J. *et al.* Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. *Cell* **185**, 2213-2233 e2225, doi:10.1016/j.cell.2022.05.017 (2022).
268 Farmer, B. C., Kluemper, J. & Johnson, L. A. Apolipoprotein E4 Alters Astrocyte Fatty Acid Metabolism and Lipid Droplet Formation. *Cells* **8**, doi:10.3390/cells8020182 (2019).
269 Hu, J. *et al.* Opposing effects of viral mediated brain expression of apolipoprotein E2 (apoE2) and apoE4 on apoE lipidation and Abeta metabolism in apoE4-targeted replacement mice. *Mol Neurodegener* **10**, 6, doi:10.1186/s13024-015-0001-3 (2015).
270 Heinsinger, N. M., Gachechiladze, M. A. & Rebeck, G. W. Apolipoprotein E Genotype Affects Size of ApoE Complexes in Cerebrospinal Fluid. *J Neuropathol Exp Neurol* **75**, 918-924, doi:10.1093/jnen/nlw067 (2016).
271 Rawat, V. *et al.* ApoE4 Alters ABCA1 Membrane Trafficking in Astrocytes. *J Neurosci* **39**, 9611-9622, doi:10.1523/JNEUROSCI.1400-19.2019 (2019).
272 Zhao, J. *et al.* APOE epsilon4/epsilon4 diminishes neurotrophic function of human iPSC-derived astrocytes. *Hum Mol Genet* **26**, 2690-2700, doi:10.1093/hmg/ddx155 (2017).

273 Arboleda-Velasquez, J. F. *et al.* Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nat Med* **25**, 1680-1683, doi:10.1038/s41591-019-0611-3 (2019).
274 Blanchard, J. W. *et al.* APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. *Nature* **611**, 769-779, doi:10.1038/s41586-022-05439-w (2022).
275 Ulrich, J. D. & Holtzman, D. M. TREM2 Function in Alzheimer's Disease and Neurodegeneration. *ACS Chem Neurosci* **7**, 420-427, doi:10.1021/acschemneuro.5b00313 (2016).
276 Zhou, Y. *et al.* Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nat Med* **26**, 131-142, doi:10.1038/s41591-019-0695-9 (2020).
277 Leyns, C. E. G. *et al.* TREM2 function impedes tau seeding in neuritic plaques. *Nat Neurosci* **22**, 1217-1222, doi:10.1038/s41593-019-0433-0 (2019).
278 Keren-Shaul, H. *et al.* A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* **169**, 1276-1290 e1217, doi:10.1016/j.cell.2017.05.018 (2017).
279 Yuan, P. *et al.* TREM2 Haplodeficiency in Mice and Humans Impairs the Microglia Barrier Function Leading to Decreased Amyloid Compaction and Severe Axonal Dystrophy. *Neuron* **90**, 724-739, doi:10.1016/j.neuron.2016.05.003 (2016).
280 Nugent, A. A. *et al.* TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge. *Neuron* **105**, 837-854 e839, doi:10.1016/j.neuron.2019.12.007 (2020).
281 Rustom, A., Saffrich, R., Markovic, I., Walther, P. & Gerdes, H. H. Nanotubular highways for intercellular organelle transport. *Science* **303**, 1007-1010, doi:10.1126/science.1093133 (2004).
282 Scheiblich, H. *et al.* Microglia jointly degrade fibrillar alpha-synuclein cargo by distribution through tunneling nanotubes. *Cell* **184**, 5089-5106 e5021, doi:10.1016/j.cell.2021.09.007 (2021).
283 Chakraborty, R., Nonaka, T., Hasegawa, M. & Zurzolo, C. Tunnelling nanotubes between neuronal and microglial cells allow bi-directional transfer of alpha-Synuclein and mitochondria. *Cell Death Dis* **14**, 329, doi:10.1038/s41419-023-05835-8 (2023).
284 Chastagner, P. *et al.* Fate and propagation of endogenously formed Tau aggregates in neuronal cells. *EMBO Mol Med* **12**, e12025, doi:10.15252/emmm.202012025 (2020).
285 Victoria, G. S., Arkhipenko, A., Zhu, S., Syan, S. & Zurzolo, C. Astrocyte-to-neuron intercellular prion transfer is mediated by cell-cell contact. *Sci Rep* **6**, 20762, doi:10.1038/srep20762 (2016).
286 Victoria, G. S. & Zurzolo, C. The spread of prion-like proteins by lysosomes and tunneling nanotubes: Implications for neurodegenerative diseases. *J Cell Biol* **216**, 2633-2644, doi:10.1083/jcb.201701047 (2017).
287 Astanina, K., Koch, M., Jungst, C., Zumbusch, A. & Kiemer, A. K. Lipid droplets as a novel cargo of tunnelling nanotubes in endothelial cells. *Sci Rep* **5**, 11453, doi:10.1038/srep11453 (2015).

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**Competing interests**

The authors declare no competing interests

**Fig. 1. Lipid metabolism and remodeling in the CNS**. The dynamic process by which the composition and structure of CNS lipids are established and modified is driven via multiple interconnected cellular pathways, occurring across essentially all CNS cell types. During de novo lipid biosynthesis (lipogenesis), acetyl-CoA acts as a substrate for the formation of new FAs and cholesterol through the fatty acid synthase (FAS) and Kandutch-Russell & Bloch pathways, respectively[231]. The FAs synthesized through these pathways, along with internalized FAs, can undergo enzymatic oxidation by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450), leading to the production of bioactive lipids. Cholesterol can also be oxidized via CYP46A1 and CYP27A1 to form 24S-hydroxycholesterol (24S-OHC) and 27-OHC, respectively. Additionally, both FAs and cholesterol can undergo non-enzymatic oxidation through free radical species, leading to the formation of peroxidated phospholipids (PLs) and products including 7α-OHC, 7β-OHC, 25-OHC, and 7-ketocholesterol (7-KC), respectively[21]. Synthesized FAs and cholesterol can also be stored in lipid droplets[21,83]. The autophagy of organelles, more specifically ER-, golgi-, lipo-, and mito-phagy, involves the incorporation of these organelles in autophagosomes. These autophagosomes then fuse with lysosomes to form autophagolysosomes, releasing lipids that can be used for various purposes[103]. Similarly, lipolysis of lipid droplet-associated neutral lipids can release substrates that can be used to synthesize and remodel other lipids (including triglycerides, plasmalogens, cardiolipins, sphingomyelin, ceramides, phosphatidylserine (PS), phosphatidylinositol (PI) and phosphatidylglycerol (PG)) in organelles and the plasma membrane[232-240]. Phospholipids are synthesized via the Kennedy pathway and remodeled through the Lands cycle to generate phospholipid diversity[116,117]. In the Kennedy pathway, a series of enzymatic reactions, operating across multiple organelles but predominantly in the ER, convert choline and ethanolamine into the phospholipids phosphatidylcholine (PC) and phosphatidylethanolamine (PE), respectively. In the Lands cycle, phospholipase A2 (PLA2) hydrolyzes a FA moiety from these phospholipids, typically releasing polyunsaturated fatty acids (PUFAs) and producing a lysophospholipid. The reacylation of lysophospholipids back to glycerophospholipids is catalyzed by lysophospholipid acyltransferases (LPLATs). LPLATs incorporate acyl chains of varying length and degrees of saturations during reacylation, resulting in the formation of structurally divergent phospholipids. While the Lands cycle is predominantly active in the ER, the enzymes involved can also be found in the Golgi apparatus, mitochondria, lipid droplets, and the plasma membrane[241,242].

**Fig. 2: Intercellular lipid transfer in the CNS**. While all CNS-resident cells can synthesize lipids through pathways mediated by sterol regulatory element-binding proteins (SREBP) and SREBP cleavage-activating protein (SCAP), intercellular lipid transfer is thought to be key in maintaining lipid homeostasis in the CNS. In pathological conditions, especially when reactive oxygen species (ROS) are elevated, astrocytes convert blood glucose to lactate, which is then transported to neurons and converted to fatty acids (FAs; light blue boxes)[157,159]. Reciprocally, neurons expel peroxidated lipids, formed through peroxidation by ROS, which are taken up by astrocytes and stored in lipid droplets (LDs) [90,157,159]. This intercellular

lipid transfer, along with astrocytic lipid droplet formation and β-oxidation, depends on apolipoprotein E (APOE)-containing high-density lipoproteins (HDLs) and glutamate, and protects against neurodegeneration[157]. Neurons also transfer 24(S)-hydroxycholesterol (24S-OHC) to astrocytes, likely under both homeostatic and diseased conditions, resulting in the activation of nuclear liver X receptors (LXRs), which control the expression of genes involved in CNS lipid homeostasis (green boxes)[72]. Astrocytes have also been reported to transfer de novo synthesized cholesterol to neurons via HDLs, which neurons use to support their functions (dark blue boxes)[154,155]. Similarly, astrocytes transfer cholesterol to oligodendrocytes to promote remyelination following pathological demyelination[184], complementing the de novo biosynthesis of cholesterol in these cells[12]. Interestingly, during remyelination, enhanced cholesterol biosynthesis in astrocytes, followed by increased cholesterol transfer to oligodendrocytes, is inversely correlated with the activity of nuclear factor erythroid 2–related factor 2 (NRF2). This suggests that NRF2 not only serves as a master regulator of cellular antioxidant responses but also acts as a key driver of intercellular cholesterol transfer in the CNS (red boxes). Astrocytic lipid transfer is also closely associated with CNS pathology, with inflammatory mediators released by microglia, such as interleukin 1α (IL1α), tumor necrosis factor (TNF), and complement component 1q (C1q), enhancing the astrocytic loading of APOE and apolipoprotein J (APOJ) HDLs with toxic long-chain saturated FAs (SFAs) (purple boxes)[120]. Microglia also drive intercellular lipid transfer in the CNS (grey boxes). Following demyelinating events, they process damaged myelin debris and generate lipid droplets, oxysterols, and desmosterol, with the latter two metabolites activating LXRs[171,173-175]. LXR activation enhances ATP-binding cassette transporter expression, thereby facilitating APOE lipidation and the formation of HDLs that can be taken up by oligodendrocytes to aid myelin formation[25]. Similarly, microglia (and CNS-infiltrating macrophages, not shown) release extracellular vesicles (EVs) containing lipids that can be used by oligodendrocytes for the genesis of new myelin sheaths[18,188,189]. Diverse pathological parameters and environmental factors, such as neuroinflammation, aging, APOE4, oxidative stress, lipid droplet overload, and altered circadian rhythms, can impair neuron-glia and glia-glia lipid fluxes, thereby driving CNS pathologies (yellow boxes).

**Box 1: Fatty acid transport into the CNS.**

Unlike cholesterol, fatty acids (FAs) can cross the blood brain barrier (BBB) from the circulation into the CNS. While virtually all FAs can be transported into the CNS, some, particularly polyunsaturated fatty acids (PUFAs), rely entirely on transport mechanisms for their uptake. For those FAs synthesized within the CNS, the relative contributions of de novo synthesis versus uptake from the periphery as the primary route of FA supply to the brain remain poorly understood. The process of FA transport occurs through both passive diffusion and active protein-mediated mechanisms[243,244]. Specifically, FA transport and binding proteins located in the plasma membrane and cytosol are essential for mediating the transfer of albumin-, lysophospholipid-, and triacylglycerol-bound FAs across the BBB[245,246]. Given the brain's enrichment in PUFAs, their transport across the BBB has been extensively studied in both health and disease contexts[59,247-249]. The major facilitator superfamily

member MFSD2A has been identified as a key regulator of PUFA transport into the brain[250,251]. Similarly, acyl-CoA synthetase long-chain family member 6 (ACSL6) regulates the activation and intracellular retention of PUFAs, docosahexaenoic acid (DHA) in particular, by attaching them to coenzyme A (CoA) to form acyl-CoA, thereby facilitating their transfer into the CNS[252]. Like PUFAs, short-chain FAs (SCFAs) such as acetate (2 carbon atoms), propionate (4 carbon atoms), and butyrate (6 carbon atoms), which are produced by intestinal bacteria through the fermentation of non-digestible dietary polysaccharides, can cross the BBB[253,254]. The entry of SCFAs into the CNS is hypothesized to be facilitated by endothelial monocarboxylate transporters (MCTs)[255]. The accumulation of microbiota-derived SCFAs in the brain provides a molecular mechanism for the dietary and microbiota-mediated regulation of CNS metabolism and physiology (reviewed in REF [256]). Using an *in vitro* BBB model, a pivotal role for cluster of differentiation 36 (CD36), fatty acid transporter protein 1 (FATP1) and FATP4 in facilitating the translocation of various FAs across the BBB has been revealed[245]. Increased desaturation improved the ability of FAs to cross the BBB, suggesting that there may be preferential PUFA entry into the CNS and offering a plausible explanation for the high PUFA content of the brain.

**Box 2: Apolipoprotein E lipidation and uptake in Alzheimer disease**

As cholesterol is insoluble in water, it binds to lipoproteins for transportation within and between cells. Within the CNS, the lipoprotein that cholesterol mainly combines with is astrocytic apolipoprotein E (APOE)[257]. The lipidation of APOE by cholesterol is mediated by lipid efflux proteins (specifically ATP-binding cassette (ABC) transporters) on the membranes of glial cells[258], resulting in the formation and release of high-density lipoprotein (HDL)-like particles (see the figure)[259]. APOE lipidation allows it to interact with endocytic receptors, such as triggering receptor expressed on myeloid cells 2 (TREM2), low-density lipoprotein (LDL) receptor (LDLR), and LDLR-related protein 1 (LRP1), which are expressed by neurons, microglia, and oligodendrocytes[30,260-262]. The binding of lipoproteins to these receptors and their uptake activates signaling cascades and provides an essential source of cellular cholesterol, complementing de novo synthesis[147,183,263-265]. Supporting the importance of APOE-mediated cholesterol transfer in maintaining CNS lipid homeostasis, the APOE4 isoform is a strong risk factor for late-onset Alzheimer disease (LOAD), with homozygous APOE4 carriers having a 14-fold increased risk of developing LOAD compared to APOE3 carriers[266]. Amongst other processes, APOE4 dysregulates intracellular lipid processing, lipid efflux, and the binding of APOE to and endocytosis by recipient cells[152,267-274]. Similarly, Alzheimer disease (AD)-associated mutations in the gene encoding TREM2, particularly the R47H missense mutation, result in an increased risk for LOAD[275]. *TREM2* mutations impair the binding and uptake of amyloid-β (Aβ) that is complexed with lipoproteins by microglia, thereby increasing amyloid pathology[264]. In parallel, *TREM2* deficiency and the *TREM2*$^{R47H}$ variant suppress the transition of microglia to a protective phenotype[276-280].

**Box 3: Tunneling nanotubes and lipid transfer**

Tunneling nanotubes (TNTs) are thin, membrane-enclosed, F-Actin-rich protrusions that link mammalian cells and permit the direct exchange of various components or signals between non-adjacent cells over long distances[281]. The material transferred via TNTs can range from ions and intracellular organelles to protein aggregates and pathogens[282-287].

Several studies indicate that TNTs are essential for maintaining CNS homeostasis and limiting CNS tissue damage in neurodegenerative disorders, particularly in Parkinson disease (PD). For example, in a mouse model of PD, microglia jointly degrade fibrillar α-synuclein intercellular distribution through TNTs, thereby lowering the α-synuclein burden[282]. TNTs also enable the movement of mitochondria and α-synuclein aggregates between microglia and neurons, with a preference for α-synuclein transfer from neurons to microglia and mitochondrial movement from microglia to α-synuclein-containing neurons[283]. Alongside α-synuclein transfer, the cell–cell spreading of other neurodegenerative disease-associated proteins, such as tau aggregates and prions can also be controlled by TNTs in the CNS[284,285]. Cellular overload of these pathological aggregates is postulated to leads to a cascade of reactions — such as lysosomal stress, increased formation of reactive oxygen species (ROS), and mitochondrial dysfunction — which drive the formation of TNTs[286]. This suggests interesting link between neuronal stress and hyperactivity, in which ROS and peroxidated lipids are transported from neurons to astrocytes to prevent lipotoxicity[157,163]. In future studies, it would therefore be of interest to assess intercellular transfer of peroxidated lipids or other lipids via TNTs, alongside lipoprotein-mediated intercellular lipid transfer, in stressed and hyperactive neurons.

Supporting the role of TNTs in lipid transfer between cells, TNTs have been shown to transfer lipid droplets between endothelial cells and their formation in these cells has been shown to be controlled by polyunsaturated fatty acids such as arachidonic acid[287]. Hence, TNTs could serve as biologically plausible 'highways' for the efficient transfer of macromolecules and organelles, such as lipid droplets, within the CNS, bypassing the energy-intensive and non-specific lipid remodeling and transfer pathways that involve lipid droplet breakdown, efflux, and lipoproteins. Importantly, while growing evidence underscores the role of TNTs in intercellular communication and intercellular lipid droplet shuttling, the studies that have been conducted to date were mainly limited to *in vitro* experiments, and thus their precise contribution to CNS lipid metabolism remains unclear.

Glossary

Autophagy: A cellular process in which damaged or unnecessary components of the cell are degraded and recycled within the cell through lysosomal activity.

β-oxidation: The metabolic pathway that breaks down fatty acids into acetyl-CoA units in the mitochondria for energy production.

Cholesterol: A lipid molecule synthesized in all cell types, essential for cell membrane structure, hormone synthesis, and bile acid formation.

Extracellular vesicles: Nanosized lipid bilayer particles secreted by cells that carry lipids, proteins, and RNA to distant and nearby cells, playing a key role in intercellular communication.

Fatty acid (FA): A carboxylic acid consisting of a hydrocarbon chains and a terminal carboxyl group, essential for energy storage and membrane structure.

Lipid droplets: Intracellular storage organelles primarily composed of neutral lipids such as triglycerides, serving as energy reserves.

Lipidome: The complete set of lipids in a biological system, encompassing various lipid classes.

Lipoproteins: Complexes of lipids and proteins with a hydrophobic core that transport lipids, such as cholesterol and triglycerides, through the bloodstream.

Monounsaturated fatty acids (MUFAs): Fatty acids with one unsaturated carbon bond in their hydrocarbon chain, commonly found in olive oil and avocados.

Phospholipids: Lipids containing a phosphate group, forming the structural components of cell membranes.

Polyunsaturated fatty acids (PUFAs): Fatty acids with two or more double bonds in their hydrocarbon chain, important for membrane fluidity and signaling.

Saturated fatty acids (SFAs): Fatty acids with no double bonds in their hydrocarbon chain, typically solid at room temperature and found in animal fats.

Tracer lipidomics: A method for studying lipid metabolism by tracking the incorporation of labeled lipid precursors into biological systems.

Western diet: A dietary pattern high in processed foods, fats (such as saturated fats and cholesterol), sugars, and low in fiber, commonly associated with various chronic diseases.