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*Review Article*

# Function and Comorbidities of Apolipoprotein E in Alzheimer's Disease

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Alzheimer's disease (AD)—the most common type of dementia among the elderly—represents one of the most challenging and urgent medical mysteries affecting our aging population. Although dominant inherited mutation in genes involved in the amyloid metabolism can elicit familial AD, the overwhelming majority of AD cases, dubbed sporadic AD, do not display this Mendelian inheritance pattern. Apolipoprotein E (APOE), the main lipid carrier protein in the central nervous system, is the only gene that has been robustly and consistently associated with AD risk. The purpose of the current paper is thus to highlight the pleiotropic roles and the structure-function relationship of APOE to stimulate both the functional characterization and the identification of novel lipid homeostasis-related molecular targets involved in AD.

## 1. Introduction

Cardiovascular diseases (CVDs), a group of disorders involving the heart and blood vessels, are currently the world's leading cause of death and the top ranking therapeutic category in terms of prescription drug spending. However, given the alarming aging of the population and the increase longevity of humans, Alzheimer's disease (AD) and other related dementias are set to become the next great health crusade of the coming decades [1]. Interestingly, these progressive degenerative disorders share common etiological grounds: advancing age, apolipoprotein (apo) E4 inheritance, cigarette smoking, high blood pressure, diabetes, obesity, oxidative stress, and abnormal blood cholesterol levels all concur to increase one's liability to develop CVD [2, 3] and dementias [4]. While the connection between vascular factors and cognition remains obscure, converging evidence associates the deficiency of APOE with impaired cognition (see Section 4). Importantly, APOE is the only locus known to significantly contribute to the risk of developing the late-onset form of AD, with the E4 and E2 alleles, respectively, increasing and decreasing the risk level [5–7]. Given its pleiotropic function (see Sections 2 and 3), the mechanisms by which APOE may exert its effects remain unclear. Yet, APOE primarily functions as a major lipid transporter in the periphery and as the main one in the central nervous system (CNS), putting lipid homeostasis center stage for the maintenance of cognitive function and the promotion of AD (see Section 3). Accordingly, alterations in lipid homeostasis are known to severely impair neuronal function and elicit progressive disorders such as Farber's, Gaucher and Niemann-Pick type C diseases [8–10]. In addition to its association with AD, APOE genotype also correlates with a wide range of other dementias and neurodegenerative disorders (see Section 5). These converging findings strongly support the implication of cholesterol/lipid metabolism as a key factor in neurodegenerative disorder etiology, a concept still under-studied in the field of AD. To stimulate interest in identifying novel, lipid homeostasis-related molecular targets involved in AD pathogenesis, this paper reviews the latest advances and concepts associated with APOE functions.

## 2. Structural Organization and Toxicological Properties of the APOE Protein

*2.1. Association between APOE and AD: Two Antipode Isoforms.* The APOE gene is mapped onto chromosome 19 and mainly exists in humans as three possible isoforms differing from each other by single amino acid substitutions at positions 112 and 158. APOE isoforms are unevenly distributed in the general population as 77% of people carry the E3 allele, 15% the E4 allele, and 8% the E2 allele [5, 11]. Second only to aging, APOE is now recognized as the most important risk factor for the late-onset form of AD. Indeed, in addition to numerous case control studies [5, 6, 12] several independent genome-wide association studies (GWASs) have been performed in homogeneous and heterogeneous population of AD and age-matched control cases in North America, Europe, and Asia [13–17]. Using genome-wide statistical criterion, the APOE4 allele was found to be associated with AD in all these independent studies. Accounting for as much as 50% of the genetic variation in liability to develop AD [18], carriers of the APOE4 allele who develop AD do so at an earlier age at onset and exhibit higher levels of soluble beta-amyloid (A$\beta$) peptide, increased senile plaque (SP) [19], and neurofibrillary tangle (NFT) accumulation, as well as more extensive cholinergic deficits [20–22].

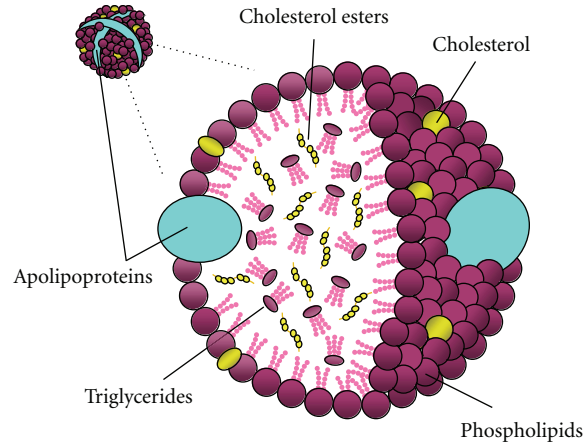
In contrast, the APOE2 variant is associated with a marked risk reduction of AD [7]. Indeed, carriers of the APOE2 allele have less AD pathological changes than APOE3 carriers, that is, less pathological A$\beta$, SP, and NFT levels [23–26], as well as larger regional cortical thicknesses and volumes indicative of greater brain reserve against cognitive decline [27]. These diametrically opposite effects of APOE4 and APOE2, which only differ by subtle amino acid substitutions at positions 112 and 158, sparked a large interest in understanding how these proteins differ at the molecular level.

*2.2. APOE Basic Structural Arrangement.* APOE is a major protein constituent of plasma and CNS lipoproteins (see Box 2.2.1) and functions primarily as a lipid transporter in the human body. Through its binding to members of the low-density lipoprotein receptor (LDLR) family present on the plasma membrane, APOE effectively mediates the uptake of lipoproteins by cells [28, 29] or activate signalling pathways that modulate lipid homeostasis [30]. At physiological levels, a substantial amount of APOE is bound to lipoprotein, whereas a significant fraction of APOE could be associated with cell surface proteoglycans in a lipid-free state [31]. As will be discussed in more detail below, these lipid-bound and lipid-free conformational states likely affect the biological functions of APOE.

In the lipid-free state, the APOE protein (299 residues) is organized as two independently folded domains linked by a protease-sensitive loop (Figure 1): an N-terminal (NT) domain (residues 1–191) comprised of a four-helix bundle [32, 33] and a C-terminal (CT) domain (residues 210–299) whose structural organization has still not been elucidated despite the crystallization of a proteolytic fragment comprising residues 223–272 [34]. The NT domain was shown to bear the LDLR binding site [28, 35–37], whereas residues within the lipid-binding CT domain mediate the lipoprotein binding [38–40] and the APOE self-association sites [31, 41, 42] (Table 1). Indeed, at physiological concentrations (micromolar), APOE exists predominantly as a tetramer [43]. Latest results indicate that, in a lipid-free state, the CT domain of APOE forms dimer, which then dimerizes further to form a tetramer [31]. However, APOE is likely to bind to lipid from its monomeric rather than tetrameric state. The transition from lipid-free to lipid-bound APOE may thus involve the formation of multiple intermediate conformational states [44].

As suggested by the initial discovery that only lipid-bound APOE binds to LDLR with high affinity [45], the structural organization of the APOE protein significantly changes when bound to lipids or lipoproteins [44, 46, 47]. Importantly, APOE adopts many lipid-bound conformations that depend on lipoprotein size [48], lipid composition [49] and on the presence of other apolipoproteins [50]. Interestingly, recent evidence indicates, however, that dipalmitoylphosphatidylcholine-(DPPC-) bound APOE adopts an alpha-helical hairpin conformation in the shape of a horseshoe, with the CT domain oriented toward the lipoprotein surface [44, 51, 52] (Figure 1). This hairpin conformation puts all the known elements of the LDLR binding site into a structural apex, potentially explaining why only lipid-bound APOE binds to LDLR with high affinity [44, 51].

*2.2.1. Box 1*




Lipids are hydrophobic molecules that use lipoproteins to move through aqueous environments. These lipoprotein particles comprise a nonpolar core of triglycerides (TGs) and cholesterol esters surrounded by an outer shell of phospholipids, cholesterol, and apolipoproteins that confer water solubility on the lipid constituents. In the periphery, lipoproteins are classified into four major classes on the basis of their associated apolipoproteins and their lipid content: chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein

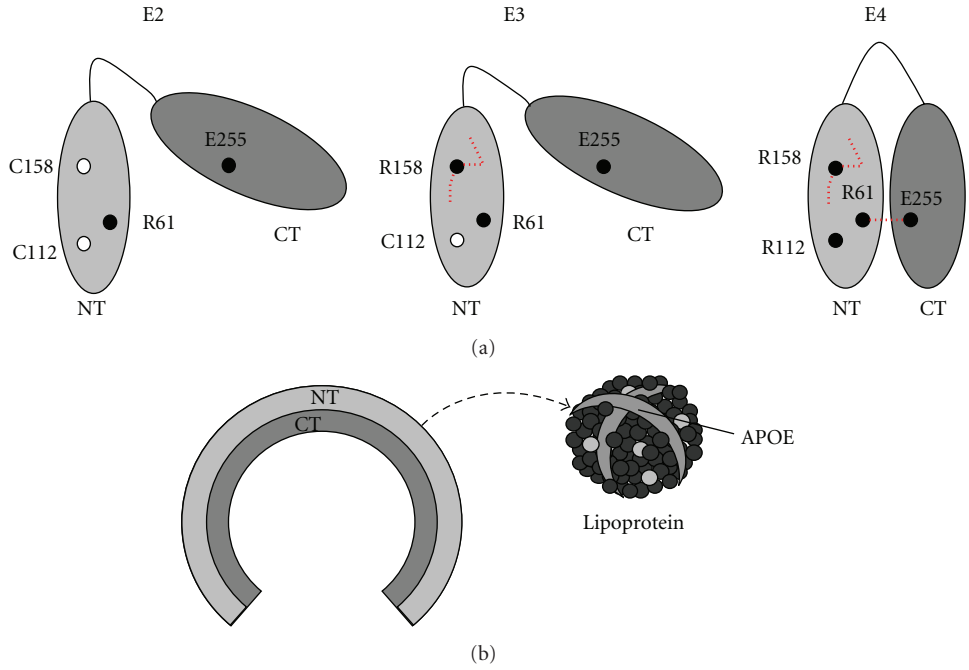



Figure 1: Illustration of the lipid-free (a) and DPPC-bound (b) conformational states of APOE isoforms. (a) In a lipid-free state, the NT and CT domains of APOE interact with each other. (b) The tridimensional conformation of APOE significantly changes when bound to lipid and adopts the shape of a horseshoe, with the CT domain oriented toward the lipoprotein surface. APOE or E: apolipoprotein E; the red dots line represents salt bridges; C: cysteine; R: arginine; E: glutamate; DPPC: dipalmitoylphosphatidylcholine; NT: N-terminal domain containing the low-density lipoprotein binding sites; CT: C-terminal domain comprising the lipoprotein binding and APOE self-association sites.

Table 1: Key structural and functional differences between the three main human APOE isoforms.

| Description | E2 | E3 | E4 |
|---|---|---|---|
| Primary sequence difference | C112 | C112 | **R112** |
| | **C158** | R158 | R158 |
| Structure particularity | Disruption of salt bridge network in the NT domain | | Domain interaction (creation of salt bridges R112-E109 and **R61-E255**) |
| LDLR binding | <2% normal receptor binding activity | High | High |
| Lipoprotein binding | HDL | HDL | VLDL/LDL |
| Protein stability | +++ | ++ | + |
| Molten-like-globule propensity | + | ++ | +++ |

E: glutamate; C: cysteine; R: arginine; LDLR: low-density lipoprotein receptor; HDL: high-density lipoprotein; VLDL: very-low-density lipoprotein; +/++/+++, respectively, low/medium/high.

(HDL) [53]. Chylomicrons are rich in APOB and represent the larger lipoproteins. Their function is that they carry exogenous (dietary) fatty acids from the intestine to the liver, skeletal muscles, and adipose tissues. VLDLs are assembled in the liver with TG, APOC, B, and E and ensure transport of endogenous lipids from the liver to adipose tissues. Once in the circulation, VLDLs undergo important TG hydrolysis, and their apolipoproteins (except APOB) are progressively eliminated. When cholesterol content becomes greater than the content of TG, VLDLs are converted into LDL with APOB as their main apolipoproteins. LDLs are taken up by the liver and other tissues through LDL receptor-(LDLR-) mediated endocytosis. Finally, HDLs are the smallest but the densest lipoprotein particles because they associate with the highest proportion of apolipoproteins, mainly APOA-I. Contrary to the other lipoproteins, HDLs mediate the reverse cholesterol transport as they extract cholesterol from peripheral tissues and transport it to the liver for excretion. In the CNS, only HDL-like lipoproteins composed primarily of APOE, APOA-I, and APOJ are present [54, 55].

*2.3. Structural Arrangement and Toxicological Properties of the APOE Isoforms: Understanding the Antipodes.* The APOE

protein is polymorphic, with three common isoforms bearing identical CT domain primary structure, but distinct NT domain sequence: at positions 112 and 158, E2 has cysteines, E4 has arginines, and E3 has a cysteine and an arginine, respectively [32, 56, 57] (Figure 1, Table 1). These particularities profoundly affect the structural and functional properties of APOE (reviewed in [44]).

For instance, while APOE3 and APOE4 bind to LDLR with similar affinities, the APOE2 isoform has less than 2% of the LDLR binding activity of APOE3, at least in peripheral cells [58, 59]. This inhibition of the LDLR binding activity is mediated not only by the arginine-to-cysteine substitution at position 158, which disrupts the salt bridge network between residues R92, E96, R103, R150, D151, and D154 [33], but also by part of the CT domain [59] (Figure 1, Table 1). Consequently, a double dose of APOE2 is associated with type III dyslipidemia, a disorder characterized by increased plasma levels of cholesterol and triglycerides as well as premature CVD resulting from a defective clearance in chylomicron remnants [29, 60].

For its part, the cysteine-to-arginine substitution at position 112 in the APOE4 NT domain induces the formation of a salt bridge between arg112 and glu109, modifying the orientation of the side chain of arg61, which subsequently forms a salt bridge with glu255 in the CT domain [39] (Figure 1, Table 1). This *domain interaction* apparently influences the binding kinetics of lipid-free APOE to lipids, thereby contributing to APOE4 preferences for VLDL and LDL particles, whereas APOE3 and APOE2 isoforms preferentially bind HDL particles [38, 39, 50, 61] (Figure 1, Table 1).

As aforementioned, APOE undergoes as extensive conformational changes upon binding its ligand (lipid or lipoprotein), and the transition from lipid-free to lipid-bound APOE can be facilitated thermodynamically by the formation of intermediate, partially unfolded APOE conformational states [44]. These partially unfolded structures, also called *molten-globule-like conformations*, are believed to be crucial for lipid binding by numerous apos, including APOE, apoAI [62], and apoAII [63]. Yet, molten-globule-like conformations are more prone to proteolysis, more vulnerable to degradation pathways and have been implicated in several diseases [44, 64]. Accordingly, the AD-associated APOE4 isoform possesses the highest propensity to form molten globule-like conformations, followed by APOE3 and finally, APOE2 [65] (Table 1). Conversely, APOE2 possesses the highest resistance to thermal and chemical denaturation, followed by APOE3 and APOE4 [66–68] (Table 1). In accordance with their disparate protein stability, APOE2 is associated with the highest levels of APOE lipoprotein, whereas APOE4 is associated with the lowest in both the blood and brain [69–72].

The lower stability of APOE4, its increased susceptibility for proteolysis as demonstrated by turnover studies in humans [73] and APOE human knockin mice [74] and its higher propensity to form molten-globule-like intermediates that actively bind to phospholipids and membranes could, in concert with fibrillar A$\beta$, promote lysosome leakage and apoptosis through lysosomal membrane disruption [75, 76]. The suboptimal features of APOE4 might also promote neurotoxicity and neuroinflammation through the proteolysis of APOE4 into putative neurotoxic NT and CT fragments, a process postulated to occur solely in neurons and not in astrocytes [77]. Furthermore, this proteolytic processing of APOE is proposed to occur only in the secretory pathway, and not in the internalization pathway of neurons (i.e., there is no fragmentation of the astrocyte-derived APOE acquired by neurons following internalization of APOE-lipoproteins) [77]. However, synthesis of APOE by neurons remains to be clarified (see Section 3) through additional studies both, in model systems and in humans.

In sum, studies on the conformational structure of APOE have yielded valuable insights into the relationships that exist between the structure and function of APOE. A noteworthy finding from such studies that resulted in our further understanding of APOE4's toxicological properties is that of apoE4's domain interaction, which promotes the formation of molten-globule-like conformations. Although progress has been made toward understanding how the structural differences of the three APOE isoforms relate to phenotype and disease, much work remains to be done.

## 3. Biological Functions of APOE and Interaction with Its Associated Partners

*3.1. An Evolutionary Perspective.* APOE3 allele appears to have spread during the later stages of human evolution after originating from the ancestral APOE4 allele. According to DNA sequences representing four distinct ethnic groups, APOE3 is estimated to have spread some 225,000 years ago. The depth of the tree is estimated at 311,000 years ago (range 0.176–0.579) [78]. Although these sequences analyses do not inform us of when APOE3 originated as a mutation, they imply that APOE3 arose before anatomically modern Homo sapiens first migrated from Africa about 100,000 years ago. Thus, APOE3 was present in Neanderthals (from 300,000 years ago) and in earlier African or European Homo from which Homo sapiens is thought to have diverged. Only one APOE genotype has been reported in chimpanzees and other primate species, which closely resembles human APOE4 with arginines at positions homologous to amino acids 112 and 158 (Table 2) [79–81]. Many other mammals, including rats, mice, pigs and cows, also have arginines at these positions [80]. Given the depth of human APOE genealogy tree and the similarities between human APOE4 and mammal APOEs, the APOE4 is considered as the ancestral allele in primates [79, 80].

*3.2. APOE in Cholesterol and Phospholipid Transport.* APOE is the major apolipoprotein in the CNS and plays a central role in lipid transport in the nervous system [82]. The dependence of brain cells toward APOE as their chief lipid carrier and provider is emphasized by the complete absence of synthesis of other key plasma apolipoprotein such as apoA1 and apoB in the CNS [83]. In the brain, APOE is produced mainly by astrocytes [83–86] and to a lesser extent by microglia [87]. Initial studies investigating the site of APOE production in the brain suggested that only astrocytes,

Table 2: APOE polymorphisms in humans and species differences.

| ApoE residue (+signal peptide) | Population prevalence (%) | 112 (130) | 158 (176) |
|---|---|---|---|
| Human | | | |
| APOE2 | 8 | C | C |
| APOE3 | 77 | C | R |
| **APOE4** | **15** | **R** | **R** |
| Chimp | 100 | R | R |
| Gorilla | 100 | R | R |
| Orangutan | 100 | R | R |
| Mice | 100 | R | R |
| Rats | 100 | R | R |

APOE: apolipoprotein E; C: cysteine; R: arginine.

oligodendrocytes, and ependymal cells synthesized APOE [86, 88]. Under diverse physiological and pathological conditions, neurons have also been reported to express APOE, albeit at a much lower level than astrocytes, in humans [89], neuronal cell lines [90–92], mice [93], and APOE transgenic mice [94]. Surprisingly, a significant number of studies failed to observe the *synthesis* of APOE in neurons both in rodent and human brains [20, 86, 95–99]. Clearly, additional studies are needed to clarify the issue of APOE synthesis within neurons, especially since numerous studies found no evidence of APOE mRNA expression within neurons [86, 95, 100, 101].

Cholesterol homeostasis in the CNS is regulated independently from the periphery due to the presence of the blood-brain barrier (BBB) which prevents the plasma cholesterol from crossing into the CNS [102]. Maintenance of the cholesterol pool in the brain is based on the regulation of three important steps: synthesis, transport (recycling), and excretion [103]. The first step, synthesis, is provided by *de novo* anabolism that converts acetyl-CoA to cholesterol through a series of 20 complex reactions in which 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) is the rate limiting enzyme [104, 105]. While neurons of the mature brain can synthesize cholesterol, they mainly rely on astrocytes to meet their cholesterol requirements for neuronal maintenance, growth, repair and dendritic reorganization [102, 106, 107].

Recycling of lipids reflects an energy-efficient system when compared to the biosynthesis of cholesterol because the latter involves a complex pathway requiring over 20 reactions [103, 107, 108]. Cholesterol homeostasis is maintained through a series of interdependent pathways including that of cholesterol transport in which APOE is of central significance. APOE is the primary apolipoprotein in the CNS followed by APOJ (also known as Clusterin) [109], which has also been identified as a genetic risk factor in AD by genome-wide association approaches [17, 106, 110]. In the brain, APOE is produced and secreted by astrocytes and microglia and is subsequently lipidated by the ATP-binding cassette transporter A1 (ABCA1) to form lipoprotein particles (Figure 2) [71, 102]. The role of ABCA1 is to regulate the efflux of cholesterol and phospholipids from the cell onto HDL in plasma [111]. It has been proposed that ABCA1 catalyses the initial transfer of cholesterol onto lipid-poor APOE and that ATP-binding cassette transporter G1 (ABCG1) finalizes the full lipidation of the apolipoprotein (Figure 2) [112, 113]. Although many lines of evidence support a role of ABCG1 in the regulation of cholesterol efflux, its function remains elusive. Tangier disease provides supporting evidence for the central role of ABCA1 in cholesterol homeostasis as this disease is caused by mutations in the ABCA1 gene and is characterized by HDL deficiency and cholesterol accumulation in macrophages and hepatocytes [114, 115]. Consistent with this phenomenon, ABCA1 mouse knockouts exhibit poorly lipidated APOE which in turn has been shown to influence A$\beta$ metabolism [111, 116]. The pivotal role of ABCA1 in cholesterol homeostasis makes it of potent interest as a target for AD treatment.

Following lipidation, the APOE-HDL-like lipoparticles are endocytosed by specific members of the LDLR family (including LDLR, LDLR-related protein (LRP), APOER2, and the VLDLR) present on both neuronal and nonneuronal cells (Figure 2) [102, 117]. APOE endocytosis provides cholesterol to the neuron that can subsequently be used for synthesis of plasma membranes, synaptogenesis, and dendritic proliferation [118]. The functions of APOJ in lipid homeostasis and A$\beta$ metabolism are very similar to those of APOE in that they are both carriers of cholesterol in the CNS and they both modulate amyloid fibrillogenesis and clearance [109, 119, 120]. Albeit their similar functions, APOE and APOJ are present on different HDL-like lipoprotein particles which differ in composition: APOJ-lipoprotein particles are lipid poor and have a higher phospholipid-to-cholesterol ratio compared to APOE-lipoprotein particles [85, 119, 121]. As well, there is some debate as to whether the cholesterol transport pathway used by APOE and APOJ differs since the receptor for APOJ, megalin/LRP-2, is not expressed by neurons and APOJ levels which are significantly increased in AD brain [122, 123] are unaltered in ABCA1 knockout mice suggesting that APOJ does not use ABCA1 for lipidation [111, 119, 124].

Excess cholesterol cannot be degraded in the brain due to its sterol ring. The predominant pathway to excrete cholesterol from the CNS is therefore to convert it into a more lipophilic 24(S)-hydroxycholesterol which can cross the BBB [112, 125]. This metabolite, only produced in neurons, is then directed to the liver where it can be excreted in the form of bile acids [126]. Other pathways account for about 36% of the excretion; however, the mechanisms remain unclear and controversial [125, 127].

APOE variants continue to receive great attention today and account for more genetic variance (25%) in cholesterol metabolism than any other gene [128]. APOE4/4 versus APOE3/3 carriers have 3 to 15% higher LDL and total cholesterol, depending on the population, diet, and exercise. APOE alleles show marked effects on blood lipids during dietary shifts. For example, in humans on a low-fat baseline diet, adding 300 mg cholesterol/day (2 egg yolks) caused serum total cholesterol to increase fourfold more in APOE4/4

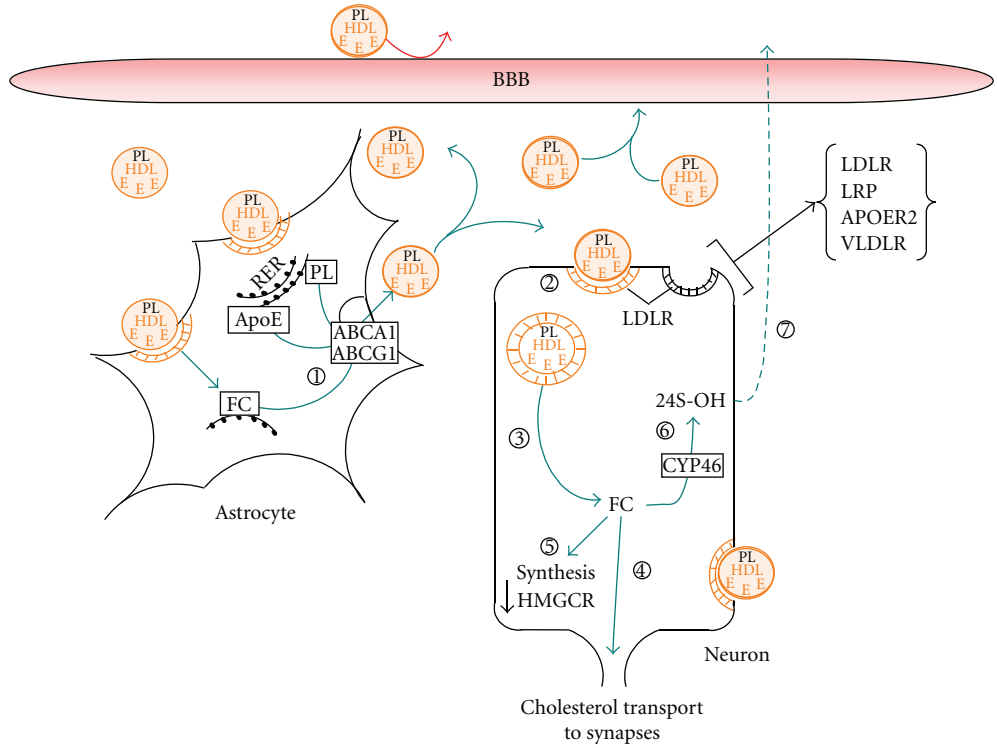



Figure 2: Cholesterol transport in the CNS. APOE is synthesized by astrocytes and assembles free cholesterol (FC) and phospholipids (PLs) to form HDL-like particles. (1) Lipidation of these lipoparticles is facilitated via the mobilization and distribution of lipids to the cell surface by ABCA1/G1. Once secreted in the extracellular space, these HDL-like particles are directed either toward the circulation through the BBB and/or to neurons requiring lipids. (2) These APOE-HDL-like particles are recognized and endocytosed by members of the cell surface LDLR family (LDLR, LRP, APOER2, VLDLR), and (3) the FC is released within neurons and can be used for neurite elongation and/or synaptogenesis (4). As a result of lipid internalization, the endogenous synthesis of cholesterol within neurons (via the HMGCR pathway) is repressed (5). Excess cholesterol will be removed from neurons through its conversion into 24S-hydroxycholesterol (24S-OH) which is mediated by cholesterol 24S-hydroxylase (CYP46) (6). This sterol can now freely cross lipophilic membranes of the BBB and exit the brain for elimination (7). APOE or E: apolipoprotein E; BBB: blood-brain barrier; RER: rough endoplasmic reticulum; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; HDL: high-density lipoprotein; LDLR: low-density lipoprotein receptor.

carriers than in APOE3/3 and even greater relative increases of LDL cholesterol [129]. As aforementioned, APOE4 preferentially binds triglyceride-rich lipoproteins (LDL and VLDL), whereas APOE3 binds preferentially to HDL [38, 39, 50, 61]. These differences in lipoprotein binding by APOE3 and APOE4 greatly influence lipoprotein clearance and the LDL/HDL ratios, which are risk factors in cardiovascular diseases. APOE4 has smaller effects on the risk of cardiovascular disease than on AD, in the range of 10% to 50%, with effects peaking during middle age [130]. In contrast, APOE4 is the most common AD risk factor throughout the world, with a 10- to 20-fold higher risk in Caucasian homozygous E4 carriers. The impact of the APOE4 variant varies widely across different populations/ethnicities, which can likely be explained, at least partly, by an interaction between genetic and environmental factors. For example, Yorubans in Nigeria showed 70% less dementia than African Americans [131], an incidence difference which may be related to their lifelong low-fat diet.

*3.3. APOE-Mediated Beta Amyloid Transport.* Because the possible roles of APOE in amyloid metabolism have been extensively reviewed recently by Kim and colleagues [106], only the potential role of APOE lipoproteins as scavengers of soluble beta amyloid (A$\beta$) peptides will be discussed in this section [21]. Indeed, evidence suggests that APOE binds avidly to soluble nonaggregated A$\beta$ fragments [6, 132]. As it was demonstrated in rat primary neuronal cell cultures, the APOE lipoproteins containing A$\beta$ may then be internalized via the APOE receptor internalization pathway [133, 134]. Following internalization, these A$\beta$ fragments could be released and degraded via the endosomal/lysosomal pathway [20, 21]. The observation that A$\beta$ reaches high intracellular concentration without affecting neuronal survival strengthens the proposed compartmentalization of internalized A$\beta$ in endosomes/lysosomes [133, 134]. Interestingly, APOE binding affinity for A$\beta$ was shown to follow an E2 > E3 > E4 gradient [135]. This provides an additional mechanism explaining, at least in part, the marked discrepancy that exists between the APOE2/E4 variants and the risk to develop AD. Indeed, the protective APOE2 variant binds A$\beta$ more avidly than the deleterious APOE4 variant and might therefore be more efficient than its APOE4 counterpart at clearing A$\beta$ fragments from the extracellular space [21].

*3.4. APOE and Neuroinflammation.* In addition to mediating the endocytosis of cholesterol and phospholipids into neurons, APOE have been associated with antioxidant properties in both *in vitro* and *in vivo* models [136, 137]. Additionally, in the periphery, APOE- and APOB-enriched lipoproteins are known to transport vitamin E and other lipid soluble antioxidant species [138]. Irrespective of APOE genotype, a plethora of oxidative reaction products has been found increased in the brains of AD and mild cognitive impairment subjects [139–141]. However, markers of oxidative damage are more intense in individuals who carry one or two copies of the APOE4 allele [137, 142].

As in many neurodegenerative diseases including Parkinson's disease [143], neuroinflammation caused by an abnormal activation of astrocytes and microglia is featured prominently as a pathological characteristic of AD [144–146]. This neuroinflammatory response is primarily driven locally by neuronal cell loss and extracellular A$\beta$ deposits evidenced by the colocalization of numerous inflammation-related proteins (i.e., cytokines, complement receptors and acute-phase proteins), activated microglia clusters, and amyloid plaques [147, 148]. *In vitro* studies affirm that A$\beta$ peptides can trigger an inflammatory response as measured by increases in standard neuroinflammatory proteins (i.e., cytokines and nitric oxide synthase) as well as nitric oxide release [149]. Neuroinflammation, especially when prolonged, is of concern for AD due to the accumulation of inflammatory molecules that are proven toxic to neurons resulting in neuronal dysfunction or death [146, 150].

As previously discussed, APOE is involved in numerous pathways influencing AD onset and progression, including A$\beta$ production, clearance, and degradation as well as its role in cholesterol homeostasis. Since the initial finding of decreased inflammation from glial A$\beta$-induced APOE production [145, 151], numerous studies have reported that APOE has an anti-inflammatory function and that its stimulation by A$\beta$ acts as a negative feedback system [145, 151, 152]. In support of this, APOE-deficient mice have a greater neuroinflammatory response relative to control mice [145]. *In vitro* studies also confirm that exogenously administered human APOE has the ability to attenuate A$\beta$-induced astrocyte activation as measured by a decrease in cyclo-oxygenase 2 (COX2) and inducible nitric oxide synthase [153] levels [145, 151]. However, the anti-inflammatory effect of APOE is reversed in the absence of an A$\beta$-induced inflammatory response as assessed by expression of interleukin-1b, a proinflammatory cytokine, following exogenously administered APOE [151]. Taken together these findings suggest a dual role for APOE in which it attenuates A$\beta$-induced neuroinflammation but also overproduction of APOE by this same activated glia can lead to an exacerbation of the inflammation [151, 154]. Although the mechanisms by which APOE influences the inflammatory response remain elusive, the primary candidate is the modulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$\kappa$B) transcription and signalling pathway [147, 155, 156].

Also investigated is whether the role of APOE in neuroinflammation is affected in an isoform-specific manner. *In vivo* studies using human *APOE* knockin mice have shown that following lipopolysaccharide (LPS) administration, APOE4 mice have a greater neuroinflammatory response relative to the APOE3 mice, suggesting that APOE4 has a less effective anti-inflammatory effect [157]. In addition to the decreased anti-inflammatory function of APOE4, cell culture studies investigating the proinflammatory function of APOE in the absence of A$\beta$ have demonstrated that astrocytes and microglia show a greater inflammatory response when exogenous APOE4 is added compared with the APOE3 isoform [151].

Collectively, these findings imply that APOE4 has a reduced anti-inflammatory effect as well as a more vigorous proinflammatory function. Although these results infer an isoform-specific immunomodulatory effect, the efficiency of APOE2 requires further investigation.

Neuroinflammation is a prominent characteristic of AD; however, it remains uncertain whether it is promoting AD progression or merely a byproduct of the disease [148]. Numerous studies have investigated the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on AD risk and treatment [158–161]. While they remain controversial, a trend toward a decrease in AD risk is observed in population-based studies with long-term use of NSAIDs, suggesting an early role of inflammation in AD [160, 162]. Recently, the NSAID risk reduction benefits have been shown to be restricted to the apoE4 carrier subgroup in the population-based Cardiovascular Health Cognition Study [163], further highlighting the interactions linking apoE metabolism to the immune system.

## 4. The Neurophysiological and Functional Correlates of the APOE4 Aging Brain

*4.1. Overview of APOE Functions.* Acting as the main cholesterol transporter of the CNS [83], APOE plays a determinant role in neuronal maintenance, growth, repair, and reorganization [164, 165]. While CNS neurons produce just enough cholesterol to survive and grow inefficient synapses [166], a glia-derived factor consisting of cholesterol complexed to APOE-containing lipoproteins strongly promotes synapse formation [107, 167]. Indeed, the formation of multiple, highly efficient synapses in the developing CNS and in the injured adult brain was shown to be highly dependent on additional cholesterol supplies provided by the glial system [107]. It is therefore understood that the plastic properties of the brain through terminal remodeling and synaptogenesis are highly dependent on CNS cholesterol bioavailability. Needless to say that ineffective cholesterol transport associated with APOE deficiencies or deficiency in one of its most important receptors, the LDL receptor (LDLR), should invariably alter plasticity-dependent cognitive refinement and synaptic remodeling.

*4.2. APOE-Deficient Mouse: A Model of Impaired Cognition.* Consistent with the human APOE4/AD observations indicating the APOE levels are tightly regulated by its polymorphisms, APOE-deficient mice which express no APOE in the brain display: (a) progressive age-related

memory loss [168–174], (b) progressive loss of cortical and hippocampal synapses that reaches nearly 70% by 18 months of age [170, 173, 175], (c) a marked reduction of cholinergic activity [176], (d) impaired injury-mediated synaptic remodeling [171], (e) impaired reinnervation processes [177, 178], and (f) deterioration of phospholipids metabolism during maturation [179]. Moreover, APOE deficiency also potentiates the detrimental effects of oxidative stress on learning/memory through the expression of inflammatory proteins in the cerebral vasculature [180]. Taken together, these APOE-deficient mouse model findings, whether through oxidative stress, altered cholinergic system function, or compromised synaptic plasticity mechanisms, all corroborate the particular susceptibility of the hippocampus to APOE deficiency in mice. Strikingly, this increased vulnerability of hippocampus-related functions to APOE deficiency is consistent with disproportionate hippocampal volume atrophy in the early stages of AD [181], particularly so in carriers of the APOE4 allele [182, 183].

Similarly, in absence of LDLR, the main receptor for APOE, synaptic remodelling, and plasticity is gravely impaired in LDLR knockout (KO) mice [184]. These mice exhibit progressive age-related memory loss and significant synaptic loss in the CA1 area (−35% at 11 months) of the hippocampus [184]. Interestingly, adult LDLR KO mice expressing no brain LDLR have a 50% reduction in APOE synthesis relative to wild-type mice [185], a feature not that dissimilar from the finding that APOE4/4 AD subjects express only 50% of the normal brain APOE levels of APOE3/3 individuals [72, 186]. Relative to wild-type mice, basal hippocampal A$\beta$1-42 are found to be significantly higher in both the LDLR KO and dual APOE/LDLR KO mice, corroborating the potential role of APOE lipoproteins as scavengers of soluble A$\beta$ peptides (see Section 3). Furthermore, the fact that the APOE4 allele and LDLR genetic variations synergistically enhance the risk of developing AD by 11-fold [187] highlights the importance of both APOE synthesis and internalization in AD. Interestingly, it was shown a few years ago that cultured astrocytes from APOE4 and APOE3 human knock-in mice synthesize and release APOE to the same extent [188]. This suggests that the reported lower levels of brain APOE protein associated with the APOE4 allele might also be mediated by the internalization of APOE within brain cells. Whether the recycling and/or degradation of the APOE4–LDLR complex is differentially regulated when compared to its APOE3 counterpart warrants further studies.

Interestingly, the introduction of human APOE3 or APOE4 in the APOE KO mice completely prevents the cognitive deficit typical of these APOE-deficient mice [189, 190]. However, it should be noted that human APOE4 expression in targeted replacement mice leads over time to (a) a marked reduction of APOE levels in the brain [191], (b) compromised synaptic plasticity [192], and (c), defective cognitive performance as well as impaired long-term potentiation (LTP) [190, 193, 194]. More interestingly, cross-breeding of the humanized APOE4 or APOE3 mice with APP717 amyloid overexpressing transgenic mice almost completely prevented the characteristic accumulation of A$\beta$ deposits reported in hippocampal and cortical areas [195]. These findings are entirely consistent with the proposed notion that brain APOE acts as a local active scavenger of extracellular A$\beta$ [132, 134].

*4.3. APOE4 and Impaired Cognition in Nondemented Individuals.* In humans, APOE4 is known to increase the risk of both familial and sporadic AD [5, 6] and to precipitate conversion to AD among mild-cognitive impairment (MCI) patients [196, 197]. MCI refers to a condition in which memory or, less commonly, another cognitive function is below normal but does not interfere with daily functioning. MCI is considered a transitional state between normal forgetfulness and AD. Moreover, converging evidence indicates that, over time, APOE4 increases the likelihood of cognitive impairments in clinically normal 50+ years old individuals [198]. Indeed, APOE4 carriers under the age of 60 years exhibited greater acceleration of age-related memory decline relative to noncarriers, despite ongoing normal clinical status [199]. This memory decline occurring prior to MCI diagnosis was previously found to be relatively specific as no differences were found in the domains of language, spatial skills, or executive function [200].

Among dominant views on what underlies this APOE4 and AD association, one is based on the observation that APOE4 proteins are the least effective in facilitating the metabolism of pathogenic A$\beta$ forms, which indirectly augments A$\beta$ burden [201]. Alternatively, another potent explanation for this increased risk of AD in APOE4 carriers is the deleterious effects of reduced protein expression on cholesterol homeostasis. Indeed, the APOE4 gene was shown to encode significantly less APOE proteins than E3/E2 counterparts, thereby providing insufficient levels of functional APOE4 to maintain CNS cholesterol homeostasis and neuronal health [134, 191, 193]. This notion finds compelling support in the neuroprotective properties of the APOE2 allele against late-life development of sporadic AD [24], as this APOE polymorphism is associated with a tenfold increase in APOE protein levels compared to both APOE3 and APOE4 [193]. Equally important is the demonstration that treatment of hypercholesterolemia with HMGCR inhibitors (statins), a family of lipids-lowering agents [27], in middle-aged individuals confers neuroprotection against late-life development of sporadic AD [202–204]. Furthermore, treatment by statins resulted in selective improvement of AD-prone hippocampal and frontal-related cognitive functions in APOE4 carriers, but without affecting CSF A$\beta$42 or total tau levels [205]. Further studies are clearly needed to assess the impact of different statin therapy regimens on histopathological hallmarks of AD-like A$\beta$ metabolism and tau deposition.

*4.4. APOE4 Effects on Hippocampal/Entorhinal Cortex Imaging and Volume Measurements.* Alongside the association between APOE4 and cognitive alterations mostly in the sphere of memory among nondemented individuals, neuroimaging studies have provided significant structural as well as functional evidence of medial temporal lobe alterations

in APOE4 carriers. While structural neuroimaging studies have yielded mixed results over the past decade, recent years have witnessed significant advances in our ability to image structural atrophy using techniques such as diffusion tensor imaging (DTI) and voxel-based morphometry (VBM). A VBM study that compared gray matter density between cognitively intact APOE4/E3 carriers and APOE3 homozygotes of all ages (age 19 to 80) showed reduced gray matter density in carriers of the APOE4 allele in right medial temporal and bilateral frontotemporal regions [206]. Another study demonstrated that the presence of an APOE4 allele in non-demented older adults was also associated with decreases in cognition joint with white/gray matter changes in the medial temporal cortex using VBM and DTI [207]. A similar VBM study more recently demonstrated that late-onset AD patients displayed a selective pattern of parahippocampal white matter loss, while early-onset AD patients experienced a more widespread pattern of posterior white matter atrophy. Among both AD groups, APOE4 positivity was associated with a greater parahippocampal white matter loss, supporting the contention that the APOE4 effect is restricted to parahippocampal white matter regions and not related to age of onset [208]. In MCI patients, left hippocampus grey matter atrophy was found to exert a stronger effect than the right hippocampus or bilateral basal forebrain in the prediction of amnestic MCI occurrence, and this left hippocampal atrophy was accentuated in APOE4 carriers relative to noncarriers [209]. This hippocampus-specific pattern of cerebral atrophy was also found in mild AD APOE4 carriers as opposed to APOE4 noncarriers who tended to exhibit greater frontoparietal atrophy [210]. In parallel, an emerging AD Neuroimaging Initiative (ADNI) study showed that APOE4 positive amnestic MCI patients with more brain atrophy were at greatest risk of functional degradation [211], highlighting the value of genetic and volumetric MRI information as predictors of disease conversion to AD.

Recent extensions to these volumetric studies described the implication of the APOE gene on brain atrophy in relation with AD cerebrospinal fluid (CSF) biomarkers levels at different disease stages. This emerging line of research finds compelling support in the recent ADNI-derived demonstration that the APOE gene reached genome-wide significance for association with CSF levels of both A$\beta$ (1–42) and tau [212]. Interestingly, another ADNI study looking to define the genetic backgrounds to normal cognition, MCI (AD disease stages), and AD in relation to CSF levels found lower CSF A$\beta$ (1–42) levels with APOE4 gene dose in each disease stage. Moreover, AD patients who were APOE4 homozygotes exhibited elevated total-tau (t-tau) and phosphorylated-tau (p-tau) 181 levels [213]. This is consistent with previous findings of a significant age $*$ APOE4 genotype interaction for p-tau231, isoprostane, and t-tau CSF concentrations increased with age [214]. In keeping with this notion, cognitively intact older adults with reduced CSF A$\beta$ (1–42) levels were more likely to be APOE4 positive (48% versus 11% in high A$\beta$ (1–42) levels older adults), to exhibit increased whole brain loss, increased ventricular expansion, and faster hippocampal atrophy rates [215]. Similarly, APOE4-related decreased CSF A$\beta$ (1–42) and increased tau concentrations were associated with significantly higher rates of brain tissue loss that were both regional as well as disease stage specific [216]. Conversely, APOE2 carriers had slower rates of hippocampal atrophy concomitant with decreased preclinical AD pathology (i.e., higher CSF levels of A$\beta$ (1–42), lower CSF p-tau and t-tau concentrations) [217]. It therefore seems that along with genetics and volumetric MRI, CSF biomarkers of AD provide valuable quantitative measurements for early detection/disease progression across disease stages.

Functional neuroimaging findings in APOE4 carriers have also abounded in the last decade. A recent study conducted with non-demented older adults found an association between APOE4 and decline in regional cerebral blood flow (rCBF) over time in brain regions especially susceptible to pathological changes in AD [218]. Accelerated rates of decline in brain functions of APOE4 carriers were suggested to contribute to an increased risk of AD and a younger age at onset [218]. These findings are based on a previous experiment conducted with a group of healthy elderly subjects among whom APOE4 carriers exhibited significantly different patterns of brain activation during a nonverbal memory task. Interestingly, these differences in brain activation were not thought to reflect task difficulty, but were rather interpreted as memory-related alterations of cognitive processing that may result from subclinical incipient AD pathology and/or APOE-related neurophysiologic heterogeneity [219]. Other evidence suggests that baseline metabolic reductions in the entorhinal cortex (EC) accurately predicted the conversion from normal aging to MCI. At follow-up, those who declined showed memory impairment and hypometabolism in temporal lobe neocortex and hippocampus particularly in APOE4 carriers [198]. These convergent cognitive and neuroanatomic findings support the notion that APOE genotype modulates the clinical phenotype of AD through influence on selective brain networks [210] and highlights the influence of genetic variance on imaging, cognitive measures, and risk for AD.

In sum, findings on the role of APOE on cognition have converged to highlight its manifest involvement in AD-prone memory and learning functions. Indeed, these APOE-related cognitive alterations were found to be concomitant with reduced cerebral metabolism, impoverished neuronal interconnections as well as damaged cerebral vasculature particularly exacerbated in medial temporal brain structures. Owing to substantial technical advances made over recent years, prevention of AD could greatly benefit from our acquired ability to relate genetic variances with abnormal brain neurophysiology patterns in cognitively intact individuals.

## 5. APOE and Other Neurodegenerative Diseases

*5.1. Other Dementias.* Next to AD, one of the leading causes of neurodegenerative dementia is Lewy body dementia (LBD). As its name clearly points on, the central pathological hallmark is the cortical Lewy bodies, as opposed to the

classical Lewy bodies described in Parkinson's disease [143], which are intracytoplasmic (ubiquitin-positive) aggregates of $\alpha$-synuclein that accumulates in the substancia nigra. While they contain less NFT, the majority of LBD brains contain as much SP as in AD brains [220]. Moreover, APOE4 is consistently found associated with LBD [221–223].

Frontotemporal dementia (FTD) represents a heterogeneous group of neurodegenerative disorders characterized pathologically by frontal and/or temporal lobes atrophy and their tau isoforms pattern. Indeed, while specific FTD tauopathies typically result from the pathological aggregation and phosphorylation of one or two tau protein isoforms, all 6 tau isoforms are hyperphosphorylated in AD (for a review of FTDs classification see [224]). The best known FTD-associated diseases that will be reviewed here for their associations with APOE are Pick's disease, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP).

Pick's disease (PiD) is characterized by ballooned neurons named Pick cells that are swollen due to the presence of cytoplasmic inclusions containing tau proteins (Pick bodies). APOE associations with PiD risk or age at onset are not consistently found [225, 226]. Of note, Farrer et al. reported that the APOE4 frequency is higher in PiD than in controls (but lower than in AD) and that the number of *APOE4* allele copies is inversely proportional to the age at onset [227]. Consistent with results from Singleton et al. study in LBD [223], Gustafson et al. also found that the APOE4 allele frequency was higher in PiD than in controls, but with APOE4/4 and APOE2 frequencies being, respectively, lower and higher than those reported for AD [228].

The next two FTDs, CBD and PSP, are also referred to as Parkinson-plus diseases due to parkinsonism symptoms. Differential diagnostic between AD, CBD, PSP, and PD is clinically difficult. However, CBD and PSP pathologies manifest themselves in tau-positive astroglial and neuronal inclusions. CBD and PSP differ both by the form of their tau inclusions—namely, "doughnut-shaped" in CBD as opposed to "tuft-shaped" in PSP—and by their intracerebral distribution [229]. Two studies illustrate particularly well the controversy about APOE4 association with CBD. On one hand, Pickering-Brown et al. did not find any association between APOE4 and clinical expression of CBD [226]. On the other hand, Schneider et al. reported a higher APOE4 allele frequency in 11 CBD cases [230]. To date, evidence of an association between PSP and APOE genotype is scarce, mostly due to small sample size [226, 231–235]. However, a higher frequency of the APOE2 allele (but not the APOE4 allele) in PSP relative to controls was found in a Japanese population [236].

Parkinson's disease, 2nd age-related neurodegenerative disorder in importance after AD and 1st extrapyramidal disorder, is also associated with dementia. Parkinson's disease dementia (PDD) accounts for 0.2 to 0.5% of dementia cases in the general population over the age of 65 and affects 24% to 31% of PD patients [237]. The risk of dementia is 4 to 6 times higher in PD patients than in controls [238]. More than one-third of PD patients meet criteria for AD and the differential diagnostic between PDD with and without AD is difficult [239, 240]. These results conducted to the rise of associations studies between APOE polymorphism and PD. However, these studies have yielded mixed results. While APOE polymorphism was not associated with PD in several studies [143, 241–248], others did find associations but differed in the terms of this association. Indeed, lower E4 allele frequency and higher E4 allele frequency were, respectively, associated in sporadic and familial PD with cognitive decline [249]. Dementia in PD was repetitively associated with the E4 allele [250–253] and also with the E2 allele [254]. Age at onset appeared to be modulated by APOE genotype (earlier onset E4 > E3 > E2) [251, 252, 255, 256] and by sex [257]. Moreover, two meta-analyses sought to further corroborate the association between APOE and the risk of PD and dementia in PD. The first one [258] confirmed previous results indicating that APOE2, which is protective in AD, increases the risk of PD [254, 259]. The more recent one [260] acknowledged that APOE4 is significantly associated with an increased risk of dementia in PD but the authors warn that publication bias and heterogeneous source of data could have confounded this result.

As regard to Huntington's disease [261], another well-known neurodegenerative extrapyramidal movement disorder with neuronal intranuclear inclusion and late dementia, the APOE4 allele has been associated with a later age at onset [262], whereas the E2 and E3 alleles appear to require other factors in order to modulate age at onset [263, 264]. Finally, multiple system atrophy [265], a rare Parkinson-plus extrapyramidal disorder characterized mostly by brainstem glial Lewy body-like inclusions and subsidiary tau inclusions, has not been associated with any APOE allele [231, 232, 266].

*5.2. Other Neurodegenerative Disorders.* Amyotrophic lateral sclerosis (ALS), the most common motor neuron disease, also presents $\alpha$-synuclein-positive inclusions, and, notably, 5% of patients will develop an FTD [267]. The association between APOE and ALS risk is controversial [268–272]. Most striking results are the association with age at onset, with the APOE4 and APOE2 alleles, respectively, decreasing [270, 272] and increasing the age [270, 273], as well as the finding that APOE plasma levels (but not APOE genotype) were correlated with a faster rate of deterioration and shortened survival time [274]. Multiple sclerosis (MS) has also been tested for its association with APOE genotype given the importance of inflammation for the disease process and the affliction of the myelin, which is vulnerable to lipid deficiency. There is a relative agreement on the negative effect of the APOE4 allele on disease severity and progression rate [275–279], but a single cross-sectional study showed that homozygosis for this allele increases both the risk for and the rate of progression of MS [280]. Contradictory results to these reported findings have also been published [241, 265, 278, 281–284].

The last neurodegenerative disease investigated in this paper section is age-related macular degeneration (ARMD). ARMD is the leading cause of vision loss in the elderly in developed countries. ARMD is associated with druse, an extracellular deposit primarily composed of activated

Table 3: Summary of the most common neurodegenerative diseases of the CNS, some distinctive features, and their associations with the human APOE isoforms.

| Neurodegenerative disease | Pathological and clinical characteristics | | APOE isoform association | | | |
|---|---|---|---|---|---|---|
| | Protein deposition | Dementia | Risk[1] | Age at onset[1] | Dementia | Severity/progression rate |
| AD | Extracellular amyloid-$\beta$ ("SP") NCI tau ("NFT") | ++ | $\varepsilon4\nearrow$ (dose effect) | $\varepsilon4\searrow$ $\varepsilon2\nearrow$ (dose effect) | | |
| PiD | NCI tau ("Pick Body") | ++ | $\varepsilon4\nearrow$(4/4<, 2/2>/-AD) | $\varepsilon4\searrow$ (dose effect) | | |
| CBD | GCI (+NCI) tau ("doughnut") | ++ | $\varepsilon4\nearrow$ | | | |
| PSP | GCI (+NCI) tau ("tuft") | + | $\varepsilon2\nearrow$ | | | |
| LBD | NCI $\alpha$-synuclein ("non- classical LB") (+ SP, + NFT) | ++ | $\varepsilon4\nearrow$(4/4<, 2/2>/-AD) | | | $\varepsilon4\searrow$ survival |
| MSA | GCI (+NCI) $\alpha$-synuclein ("Papp-Lantos Body") (GCI + NCI tau) | (+) | | $\varepsilon4\nearrow$ | | |
| PD | NCI $\alpha$-synuclein (classical LB) | + | ($\varepsilon4\nearrow$) $\varepsilon2\nearrow$ | $\varepsilon4\searrow$ (> $\varepsilon3$> $\varepsilon2$) | $\varepsilon4\nearrow$ | |
| HD | Neuronal intranuclear huntingtin | + | | $\varepsilon4\nearrow$ | | |
| ALS | (NCI TDP-43) | 5% FTD | $\varepsilon4\nearrow$ | $\varepsilon4\searrow$ $\varepsilon2\nearrow$ | | |
| MS | | | 4/4$\nearrow$ | | | $\varepsilon4\nearrow$ severity |
| ARMD | Extracellular amyloid-$\beta$ ("drusen") | | $\varepsilon4\searrow$ $\varepsilon2\nearrow$ | $\varepsilon4\nearrow$ $\varepsilon2\searrow$ | | |

AD: Alzheimer's disease; PiD: Pick's disease; CBD: Corticobasal dementia; PSP: Progressive supranuclear palsy; LBD: Lewy body dementia; MSA, multiple system atrophy; PD: Parkinson's disease; HD: Huntington's disease; ALS: Amyotrophic lateral sclerosis; MS: Multiple sclerosis; ARMD: Age-related macular degeneration; NCI: neuronal cytoplasmic inclusion; GCI: glial cytoplasmic inclusion; SP: senile plaque; NFT: neurofibrillary tangle; LB: Lewy body; ++ indicates very present, + moderately present, (+) present in a subset; [1]the parentheses indicate that the association is less consistently found.

complement components, A$\beta$ peptide, APOE, and ubiquitin. It is noteworthy that the molecular composition of the drusen is highly similar to that of the SP found in AD. Interestingly, AD and ARMD also share some cardiovascular risk factors. These evidence prompted association studies between APOE genotype and ARMD. Two associations were reproductively observed: the *APOE4* allele is less frequent among ARMD patients [285] and reduces the risk of developing the disease by up to 40%, whereas the *APOE2* allele is more frequent and increases the risk by up to 20% [286]. Kovács et al. stressed the opposite frequencies between *APOE4/APOE2* and ARMD/AD and highlighted the rare occurrence of ARMD among AD patients [287]. As for Baird et al., they pointed that APOE is the most consistently associated gene with ARMD. They showed that *APOE4* is protective against ARMD and/or increases its age at onset, whereas *APOE2* decreases the age at onset of ARMD [288]. Interestingly, Malek et al. presented a mouse model of ARMD in which aged human APOE transgenic mice were fed a high-fat cholesterol-rich diet [289]. They found that the mice displayed APOE isoform-dependent pathologies of different severity. Mice expressing the human APOE4 were the most severely affected ones; they developed changes that mimicked ARMD pathology, but that could not be attributed solely to age or high-fat cholesterol-rich factors.

In sum, neurodegenerative diseases, with or without dementia, encompass a large spectrum of disorders. The more we learn about these pathologies, the more similarities and differences are found, which result in a constant reclassification of these diseases. One common pathological hallmark is the deposition of misfolded protein (amyloid-$\beta$, tau, $\alpha$-synuclein, etc.). Through the modulation of disease risk, age at onset, and/or rate of progression, APOE is involved in an isoform-dependent manner in all the diseases reviewed here (Table 3). With the noticeable exception of ARMD, the APOE4 allele is predominantly deleterious, whereas the APOE2 is beneficial. This evidence suggests that APOE polymorphism confers a risk susceptibility not specific to AD, but to neurodegenerative disease in general.

## 6. Conclusion

We have reviewed the postulated roles of APOE4 in the development of different forms of dementia and particularly, in sporadic AD. While age remains a key determinant that modulates the onset and expression of AD pathology, genetic risk factors such as APOE4 appear to play a central role in the pathophysiology of this disease, years, if not decades, before clinical diagnosis. The combined use of genetic profiling and gene targeting will allow scientists to better target the biochemical mechanisms regulating the loss of synapses and the accumulation of amyloid deposits in the aging and diseased brain. The discovery that compounds such as estrogens, probucol, indomethacin, and even rosiglitazone can significantly induce APOE synthesis and secretion both *in vitro* and *in vivo*, and enhance cognitive performances [290–294] in small clinical trials certainly suggested a potential therapeutic role for APOE modulators in AD. The surprising convergence of these biochemical, pharmacogenomic, and clinical observations raises exciting new possibilities and certainly interesting new therapeutic avenues for the treatment and prevention of a genetically-defined, sizeable subset of Alzheimer's disease subjects.

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